

BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE



MARCH 1949

PRESIDENTIAL ADDRESS*

BENJAMIN P. WATSON

President, The New York Academy of Medicine

FELLOWS of The New York Academy of Medicine: I thank you for the great honor you have conferred upon me in electing me your President. I accept office with very mixed feelings: First, there is that of intense pride that you should have considered me worthy, but there are also those of deep doubt and misgiving as to my ability to give the standard of service expected of me and set by my predecessors. I can only pledge you my utmost effort.

Fortunately, while the Presidency changes every two years, the Trustees, the Council, our great Committees of Library, of Public Health Relations, of Medical Education and of Medical Information have continuity of Service.

It is to the Chairmen, members and permanent officials of these and of the other Committees that I shall turn for information and enlightenment. There is also immeasurable satisfaction in the knowledge that we have in our Director, Dr. Howard Reid Craig, an able and devoted administrator.

With all of these to guide me and through my contacts with individual Fellows I hope that I shall reflect in everything I may be called

* Given January 6, 1949 at the Annual Meeting of The New York Academy of Medicine.

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VOLUME 25

1949

BULLETIN OF THE NEW YORK
ACADEMY OF MEDICINE

CONTENTS

- Opening Address, 21st Graduate Fortnight 3
George Baehr

- The Use of Antiepileptic Drugs 5
H. Houston Merritt

- The Present Status of Liver Function Tests Including
Observations on the Newer Flocculation Procedures 16
Maurice Bruger and Elliot Oppenheim

- Review of Studies on Blood Sugar 32
Edward Thomas Waters, Ph.D., D.Sc.

Discussions by
*Frederick M. Allen, Edward S. Dillon,
Thomas H. McGavack and Charles H. Best*

Library Notes:

- Address of Acceptance and Appreciation of the
Gift of the Edwin Smith Papyrus 60
George Baehr

- Recent Accessions to the Library 61
-

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MAHLON ASHFORD, *Editor*

Published Monthly by THE NEW YORK ACADEMY OF MEDICINE
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BULLETIN OF
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JANUARY 1949

ADVANCES IN THERAPY*

GEORGE BAEHR

THIS is the first Graduate Fortnight of the Academy devoted to a general review of recent Advances in Therapy. The preceding twenty annual Graduate Fortnights have each been devoted to a consideration of the diseases of one anatomical system, such as the cardiovascular or to one specific field of medicine such as the infections or neoplasms. In breaking with tradition, the Committee on Medical Education of the Academy and its subcommittees on the Graduate Fortnight have been moved by the remarkably rapid advances in the field of therapy within the last decade, which have left large gaps in the knowledge of all physicians who received their undergraduate and post-graduate training in medicine even as recently as ten or twenty years ago.

During my own early years of medical practice, therapy other than surgical was largely palliative or psychological or directed to the alleviation of symptoms. Only a half dozen diseases yielded to specific forms of therapy and these were crude and imperfect. Empiricism was still the order of the day. There is small wonder that many of us, following the lead of Skoda of an earlier and still more empirical gen-

* Opening address, 21st Graduate Fortnight of The New York Academy of Medicine, October 4, 1948 by the President of the Academy.

eration, were therapeutical nihilists who found it more fruitful to concentrate our efforts upon refinements in medical diagnosis and on the laboratory techniques of bacteriology, pathology and biochemistry which were aids to a better understanding of fundamental disease processes. In the wards and laboratories of the hospitals we sought to improve the accuracy of our diagnosis and tried to unravel the mysteries of etiology and pathogenesis.

As I look back over those days, I appreciate that we were laying the groundwork of medicine in preparation for the new era of therapy in which we are now entering. And yet, I must admit, that our intense concentration upon these fundamentals was in part an escape from that discouraging sense of therapeutic helplessness and blank futility which came over us daily as we moved from bed to bed and confessed our inability to end or even shorten most of the diseases which confronted us.

How the picture has changed in an incredibly short time! The great advances in therapy which will be reviewed during this Fortnight are only a forecast of more and better therapeutic discoveries in the immediate future. A new vista of therapeutics has been revealed to us in the last decade or two through discovery of the antibiotics, the anticoagulants, the antihistamine drugs, the new and powerful hormonal agents with which the physiology of all organs and tissues of the body can be modified, the new knowledge of the amino acids, minerals and vitamins which give us the means to maintain or restore the nutritional state of the body in health and disease, the new radioactive materials. These are a few of the additions to our therapeutic armamentarium which are responsible for a significant and progressive reduction in mortality and an abbreviation of morbidity.

The evening lectures of the Fortnight, the morning discussion panels, the afternoon clinical demonstrations at the great hospitals of the city and the remarkable teaching exhibit which has been assembled at the Academy, provide an unrivalled opportunity for all members of the medical profession to bring their knowledge of modern therapeutics up to date, so that they may serve the people in accordance with the best modern standards and prepare themselves for even greater advances in therapy which are yet to come.

THE USE OF ANTIEPILEPTIC DRUGS*

H. HOUSTON MERRITT

Professor of Neurology, Columbia University, College of Physicians and Surgeons
and Director of the Service of Neurology, Neurological Institute

THE USE OF anticonvulsant drugs is only one part of the treatment of patients with convulsive seizures but at the present time, they are the most important single factor in the treatment of such patients. Success or failure in the treatment of patients with seizures depends almost wholly on the control of the attacks. In the vast majority of the cases, anticonvulsant drugs are the only means at our disposal which will prevent or lessen the frequency of seizures.

The anticonvulsant drugs which are in use at the present time can not be considered as a cure for epilepsy. Although very little is known in regard to their mode of action, it is apparent that for the most part they serve only to alter the activity of the cerebral cortex in some manner so that the tendency for the occurrence of convulsive seizures is diminished. They have very little, if any, permanent effect on the underlying physico-chemical disturbance which is responsible for seizures since cessation of a treatment, which is effective in the prevention of seizures, almost regularly results in the prompt recurrence of attacks.

In recent years there has been a revival of interest in the medical therapy of epilepsy and new drugs are being tested in various clinics throughout the country. The direct result of these studies is the introduction of more effective remedies for the prevention of attacks. Of greater importance, however, for the ultimate control of the disease is the possibility that the studies in regard to the nature of the chemical compounds, which inhibit seizures, will throw some light on the nature of the fundamental pathological physiology of the disease.

Classification of Patients with Seizures: The intelligent use of anticonvulsant drugs is dependent to a great extent on a knowledge of the type or types of seizure to which the patient is subject. This requires a brief discussion of the classification of patients with convulsive seizures.

* Presented October 5, 1948 before the 21st Graduate Fortnight of The New York Academy of Medicine. From the Department of Neurology, College of Physicians and Surgeons, Columbia University, and the Neurological Institute, New York.

There are three ways of subdividing the patients with epilepsy, all of which have some value.

The first method divides the cases into two groups, symptomatic and idiopathic, according to the presence or absence of an organic lesion. This division emphasizes the fact that a thorough study of each case is a necessary preliminary to the application of the therapy. The concept of symptomatic and idiopathic epilepsy is a fallacious one, however, if we assume that it gives us any understanding of the underlying pathophysiology of the disease. It is evident that the seizures of patients with symptomatic epilepsy are not due solely to the organic lesion in the central nervous system. This lesion is constantly present but the attacks are irregular in occurrence. On the other hand, the methods of study which are now available do not indicate whether or not there is a structural or functional abnormality of the nervous system in the patients with so-called idiopathic epilepsy. Studies of the electrical activity of the brain by the method of electroencephalography¹ almost regularly show evidence of a disturbance of the cortical activity in the moments preceding and during a seizure. In addition abnormal cortical activity can be found in the interval between attacks in a large percentage of the patients.

The second method² of dividing the cases is based to a great extent on the result of the electroencephalographic study of the patient. The occurrence of focal or generalized seizures is dependent on whether the abnormal discharge which initiates the seizure is generalized or localized to one particular region of the cerebrum. This method of separating the attacks is of special value to the neurosurgeon, who approaches the treatment of epilepsy from the surgical viewpoint. It is also of some value to the clinician in the choice of various treatment methods.

The third method of dividing the cases of epilepsy which is based on the clinical manifestations of the seizure is of particular value in the selection of the drug to be used in the therapy. Epileptic attacks may be divided roughly into three groups. Some patients may have only one type of seizure but it is not uncommon for the afflicted individual to suffer with two or even three types of spells. The three types of attacks are 1) petit mal, 2) grand mal (including Jacksonian and focal seizures), and 3) psychic equivalents or psychomotor attacks.

Petit mal seizures, which occur predominantly in children, are manifested by a transient clouding of consciousness lasting for only a few

seconds, with or without minor movements of the head, eyes, and extremities. Other features of petit mal epilepsy include transient loss of postural tone (cataplexy), myoclonic jerks, and the characteristic changes in the electroencephalogram. The phenomena which occur in a grand mal attack may be quite varied. Characteristically these attacks are ushered in by a warning (aura) and are followed by a sudden loss of consciousness with tonic-clonic spasms of the musculature, with or without urinary and fecal incontinence. The convulsive movements continue for one to many minutes and are often followed by sleep or a brief period of confusion. Jacksonian seizures are characterized by the occurrence of clonic movements of the muscles of one extremity or one-half of the face without the loss of consciousness. The clonic movements may spread from one extremity to the other or to the face. If the movements spread to the opposite half of the body, consciousness is lost and the further course of the seizure is similar to that of the usual grand mal attacks. Focal seizures are grand mal attacks initiated by some sensory or motor phenomenon which can be referred to excitation of some specific region of the brain. Psychic equivalents or psychomotor attacks are terms used to describe a heterogeneous group of epileptiform disturbances with clinical manifestations which do not conform to those of the grand mal or petit mal types of seizures. The common form of psychomotor attack is often confused with petit mal. It differs from the latter in that the duration of the period of mental cloudiness is longer and the range of muscular movements is greater, and it is distinguished from a grand mal seizure by the fact the patient does not fall to the ground in a tonic-clonic seizure with complete loss of consciousness. Rarely psychic equivalent attacks may be manifested by a clouding of the mental state for many hours during which time the patient may perform acts of which he is entirely unaware.

Historical Review of the Development of Antiepileptic Drugs: The modern approach to the treatment of epilepsy begins with the middle of the nineteenth century. While it is true that various drugs were used by the ancient and medieval physicians, the treatment methods of these times were mainly dietary restrictions, the invocation of supernatural powers and the administration of substances which had magical properties.³

The list of drugs which were used in the latter part of the nineteenth century⁴ include the bromides, opium, codeine, borax, chloral

hydrate, amylene hydrate, nitroglycerin, chloretone, zinc salts, urethane, solanum carolinense, simulo, trional, iron, coal tar derivatives (phenacetin, antipyrin and acetanilid), and chloroform. The introduction of the bromides as a therapeutic agent in epilepsy resulted from an interesting observation of Locock⁵ that the seizures in epilepsy were often related to hysteria or the menses. He prescribed bromides as a remedy in a case of epilepsy connected with sexual excitement and after all other medication had failed, the result had been an entire cessation of attacks. He had also tried the bromide of potassium in 14 or 15 similar cases, with failure in only one.

The next advance in the pharmacological treatment of epilepsy was the introduction of the use of luminal (phenobarbital) by Hauptmann in 1912.⁶ This drug which had been introduced as a sedative and a hypnotic, was administered in daily doses of 0.3 gram to patients with frequent and severe grand mal seizures and favorable results were reported. There was a reduction in the frequency of the attacks and a decrease in the severity of the attacks that did occur, and general improvement in the health and nutrition of the patients who had suffered from over-dosage of bromides. He noted that sudden withdrawal of the drug would result in the precipitation of a number of seizures.

Between 1912 and 1937 researches in the therapy of epilepsy were directed toward the modification of the internal milieu by restriction of fluids and by dietary measures rather than by the administration of drugs. In 1921 Geyelin⁷ demonstrated that fasting influenced the incidence of seizures in a certain number of the patients with epilepsy and suggested that the benefit was due to the acidosis induced by the fasting. This observation of Geyelin led to other methods of producing an acidosis. Wilder⁸ at the Mayo Clinic demonstrated that a diet high in fat and extremely low in carbohydrate was as effective in producing acidosis as fasting. Wilder proposed the diet on the theory that acetoacetic acid should behave pharmacologically as an anesthetic. Other observers believed that a high fat diet owed its therapeutic value to its action on the acid-base equilibrium by correcting an abnormal tendency toward the spontaneous development of alkalosis.

Data which showed disturbance in the water-balance in patients with epilepsy were presented by Gamble⁹ in 1923. McQuarrie¹⁰ in 1929 demonstrated that a negative fluid balance tended to reduce the frequency of seizures. The greatest advocate of the dehydration therapy,

however, was Temple Fay¹¹ of Philadelphia. The excessive restriction of fluid intake necessary to maintain a negative fluid balance negated any wide acceptance of this form of treatment.

In 1937 a new method of testing the anticonvulsive activity of drugs in animals was devised by Putnam and Merritt.¹² By this method, Merritt, Putnam and Schwab tested a large number of compounds and found a number of them to have an anticonvulsant activity greater than those already in common use. One of these compounds, sodium diphenyl hydantoinate (phenytoin sodium, dilantin sodium, epanutin) was introduced into the treatment of epilepsy in 1938¹³ The results obtained with sodium diphenyl hydantoinate has stimulated further search for more effective anti-convulsant drugs and in the past 10 years a number of new compounds have been developed.¹⁴

Use of Anticonvulsant Drugs: The drugs which are most commonly used at the present time in the treatment of patients with convulsive seizures are the bromides, barbiturates, hydantoins, and oxazolinediones. Other drugs are being subjected to experimental use but reports in regard to their efficacy are not available.

The treatment of patients with convulsive seizures can not be standardized, since each patient presents an individual problem. Some generalization can be made regarding the drugs which are most likely to be effective in the various types of seizures and in regard to the dosage to be used. A point of practical importance is that a change should not be made abruptly from one form of therapy to another. Even though two drugs apparently have similar action, the sudden replacement of one of them by another may result in the occurrence of status epilepticus. For this reason the full dosage of the first medication should be continued for several days until an adequate reservoir of the new drug has been built up in the patient's system.

Grand Mal Seizures: Phenytoin sodium and phenobarbital are the most effective drugs in the treatment of patients with grand mal seizures. Either of these two drugs can be tried as the first method of therapy. If one proves ineffective or is not tolerated, the other can be substituted or a combination of the two can be given together. Occasionally, 3-methyl-5,5 phenylethyl hydantoin (Mesantoin) or a combination of this drug with the phenytoin sodium will give the best results. Rarely the bromides or a combination of bromides and phenobarbital or phenytoin sodium will be most effective.

Petit Mal Attacks: Only rarely are any of the drugs, which are effective in the treatment of grand mal, of any value in the treatment of patients with petit mal attacks. Trimethyloxazolidinedione (tridione) is the drug of choice for the latter type of seizure. Other oxazolidinediones have been used experimentally but the reports are inadequate for satisfactory evaluation of their efficacy.

Psychomotor Attacks: The drugs which are effective in the treatment of grand mal seizures are effective in the treatment of patients with attacks of the psychomotor type. Larger dosages are required and the results are on the whole not as good as they are in the patients with grand mal seizures.

Dosages and Side-Effects of the Various Drugs. Bromides: Although any of the salts may be used, the drug is most commonly given as the sodium or potassium salt, in tablets, or aqueous solution. The average dose for an adult is 15 grains (1 gm.) three times daily with proportionate doses to children according to size. In the absence of toxic symptoms this dose can be increased to a maximum of 30 grains (2 gm.) three times daily. The chloride intake must be kept at an adequate level to prevent undue replacement of chloride ion in the body fluid by the bromide. Facilities for the determination of the bromide content of the serum should be available. The effective level may be as low as 100 mg. per hundred cubic centimeters in some patients, whereas 300 mg. per hundred cubic centimeters may not be effective in others. Toxic symptoms may develop with a concentration of 150 mg. or greater. The chief objections to the use of bromides lie in the frequency of the development of skin rash, toxic psychosis, and their reputed tendency to produce mental dullness.

Phenobarbital (Phenylethyl barbituric acid): For the average adult the initial dose of phenobarbital should be $1\frac{1}{2}$ grains daily. This can be given at bed time. If after a trial period of two weeks or as long as is necessary to determine whether this dose is effective, further increases can be made in the dosage until the patient is taking as much as $4\frac{1}{2}$ to 6 grains per day. If this amount of the drug is not sufficient to control the seizure, it is probable that a further increase will not be of value. In children, the dose of phenobarbital should be in proportion to weight, but it has been found that children are able to tolerate and require almost as large a dose as adults. It is, therefore, advisable to give children over 6 or 7 years of age the minimum dose of $1\frac{1}{2}$ grains per day. The

toxic symptoms of phenobarbital are well known and need no further discussion. Drowsiness is common at the start of the treatment but this may disappear with continued use of the medicine. Allergic skin rashes are infrequent and there are no effects on the hemopoietic system.

Mebaral: Mebaral, the 3 methyl derivative of phenylethyl barbituric acid (phenobarbital) can be used as a substitute for the latter because it has slightly less sedative effect. Approximately twice the dosage of phenobarbital is required and at this dosage the sedative effect is similar to that of phenobarbital.

Phenytoin Sodium: Phenytoin sodium (dilantin sodium). 5,5-diphenyl glycolyl urea is particularly valuable in the treatment of psychomotor and grand mal attacks. This drug has the advantage over phenobarbital and the bromides in that it has very little or no hypnotic activity. The regulation of the dosage is more difficult and minor toxic symptoms are more frequent. The toxic symptoms are not serious and it is almost impossible for a patient to take a fatal dose of the medicine.

The principle of administration of phenytoin sodium is similar to that of phenobarbital, that is, the establishment and maintenance of a reservoir of the drug sufficient to control the seizures. In the average adult, the initial dose should be $4\frac{1}{2}$ grains (0.3 gm.) daily. If any seizures occur after two weeks of this dosage, it should be increased to 6 grains (0.4 gm.) daily. Further increases in the dosage should be by increments of $1\frac{1}{2}$ grains (0.1 gm.) until the maximum dose of 9 grains (0.6 gm.) daily is reached. In the majority of adults, 6 grains (0.4 gm.) is the optimum dose. In children over 12 or 14 years, the average dose is $4\frac{1}{2}$ grains to 6 grains (0.3 to 0.4 gm.) and in younger children 3 to $4\frac{1}{2}$ grains (0.2 to 0.3 gm.). The medicine can be given in divided doses spread out through the day, or it can be given all in one dose at bed time. The drug is quite alkaline and it may cause gastric upsets. This can be prevented by giving the drug along with the meal or with some food.

The toxic symptoms of phenytoin sodium are different from those of phenobarbital in that nervousness or sleeplessness, rather than drowsiness, is more commonly an early symptom. Other toxic symptoms are gastric distress, nausea and vomiting, unsteadiness of gait, hypertrophy of the gums and dermatitis.

The minor toxic symptoms are frequently transient and may disappear with continuation of the therapy or when the dosage is tempo-

rarily reduced. Nystagmus, unsteadiness of gait and tremors of the extremities can be produced in practically all patients if the dosage is raised sufficiently high. A few adults will tolerate as much as 9 to 12 grains (0.6 to 0.8 gm.) but symptoms usually develop when the dose is increased beyond $7\frac{1}{2}$ grains (0.5 gm.) The appearance of toxic symptoms calls for a temporary or permanent reduction of the dosage. If the reduced dose is not effective in controlling the seizures and attempts to increase the dose again result in the appearance of toxic symptoms, a combination of phenytoin sodium and phenobarbital or bromides should be tried, or one of the other hydantoins, such as mesantoin, should be substituted.

Gastric discomfort, nausea, and vomiting may be controlled by the administration of the drug along with a little bicarbonate of soda or at meal time. Dermatitis of a scarlatiniform or morbilliform nature occurs within two weeks of institution of therapy in approximately 5 to 10 per cent of the patients and is accompanied by fever and an eosinophilia. The rash usually disappears within a few days after withdrawal of the drug. Recurrence of the rash when treatment is reinstituted or the development of an exfoliative dermatitis precludes further use of the medicine.

The most troublesome toxic symptom of the drug is hypertrophy of the gums. This is most common in children and varies from a slight swelling of the gums to a marked hyperplasia with almost a total covering of the teeth. The hyperplastic tissue is usually quite firm without any tendency to bleeding. The swelling of the gum tissue is not related to any disturbance in the absorption or utilization of vitamin C. This hyperplasia can be retarded by daily massage of the gums. Excessive growth of the gum tissue can be excised by the electric cautery. The development of psychotic symptoms in patients under therapy with phenytoin sodium is rare and it is usually not possible to determine whether these symptoms are related to the use of the drug or not. In such cases a change in the type of treatment should be tried.

Other Hydantoins: Various derivatives of the hydantoins have anti-convulsive properties. In some patients one of these hydantoin derivatives may be more effective in controlling grand mal or psychomotor seizures than either phenobarbital or phenytoin sodium. The work on the majority of these drugs is still in the experimental stage, with the exception of the 3-methyl, 5-phenyl, 5-ethyl derivative, which has been

given an extensive clinical trial in several clinics. The average dose for children is 0.4 gm. daily, and for adults, 0.6 gm. The maximum daily dose is 1.0 gm. The drug can be used in combination with phenytoin sodium. The most common symptom of overdose is drowsiness. Toxic skin rashes are slightly more frequent than with the use of phenytoin sodium. Blood dyscrasias have occurred in a few patients who were receiving mesantoin and other anticonvulsant drugs. It is not definitely known whether mesantoin alone has any serious toxic effect on the blood forming organs.

Tridione (3,5,5-trimethylloxazolidine-2,4 dione): Tridione is the most effective drug in the treatment of petit mal seizures. The use of this drug is accompanied by a cessation or reduction in frequency of petit mal attacks in approximately 50 per cent of the cases. In a few patients the cessation of attacks is accompanied by a decrease in the abnormalities in the electroencephalogram. In such patients it is sometimes possible to discontinue the use of the drug without recurrence of the petit mal seizures. The drug is of no value in the control of grand mal or psychomotor seizures. If patients are subject to one of the latter types of seizures as well as petit mal, phenytoin sodium or phenobarbital should be given along with the tridione.

The dosage of tridione for the treatment of petit mal varies from 0.3 to 2.0 gm. daily, starting with 0.3 gm. and gradually increasing the dose until the seizures are controlled or toxic symptoms appear. Among the toxic symptoms are skin rashes, which require a cessation of the treatment, and visual symptoms—an unusual sensitivity to light. This latter symptom is apt to develop in adolescent or adult patients and is uncommon in young children. The photophobia is not accompanied by any change in visual acuity, and it disappears when the medicine is discontinued.

Several cases of fatal aplastic anemia¹⁵ following the exhibition of tridione for periods of six and ten months have been reported. Prolonged use of the drug may also be accompanied by a decrease in the percentage of polymorphonuclear leukocytes in the blood without an absolute decrease in the total number of leukocytes. Although it is not known whether the observation of any precautions will make it possible to prevent serious or fatal changes in the blood, it is recommended that routine blood count be made monthly in patients using tridione. The drug should be discontinued if any significant changes are found.

Combination of Drugs: Since phenytoin sodium has very little sedative effect, it is particularly adapted to use in combination with phenobarbital, the bromides, or mesantoin. Various combinations can be used when one drug is not effective in controlling the seizures or when the effective dose of phenytoin sodium alone produces toxic symptoms. The doses of the combination must be worked out according to the tolerance of each patient. Three to five doses a day of a combination of $1\frac{1}{2}$ grains (0.1 gm.) phenytoin sodium with $\frac{1}{2}$ grain (0.06 gm.) of phenobarbital, 15 grains (1 gm.) sodium bromide, or 0.1 gm. of mesantoin are usually required in the more resistant cases.

Patients who are subject to petit mal seizures along with grand mal or psychomotor seizures should receive tridione plus phenytoin sodium, phenobarbital or mesantoin.

Status Epilepticus: Patients who are subject to seizures may have attacks so frequently that they do not recover from the coma produced by one attack before the next attack supervenes. The patient remains in coma for 12 to 24 hours during which time there may be many convulsive seizures. The attacks may cease spontaneously and the patient recover consciousness after a period of 24 to 48 hours, or death may occur as the result of the repeated attacks. The likelihood of the latter eventuality is so great that vigorous therapeutic methods aimed at terminating the seizures are justified. Good results in regard to termination of the attacks can sometimes be obtained by anesthetizing the patient with one of the volatile anesthetics such as chloroform or ether. Termination of the seizures is more certain with the injection of sodium phenobarbital or paraldehyde intravenously with less risk of pulmonary complications. It is important that a large dose be given at the first injection because best results are obtained when the full amount is given in one, rather than in divided doses. For status epilepticus in adults 0.4 to 0.8 gram (6 to 12 grains) of sodium phenobarbital dissolved in distilled water should be injected intravenously or 3 to 6 cc. of paraldehyde injected intravenously. The dosage for children should be from 0.2 to 0.4 gram (3 to 6 grains) of sodium phenobarbital or 2 to 4 cc. of paraldehyde according to the size of the child.

SUMMARY

The treatment of patients with convulsive seizures requires a complete study of the patient in order to determine what factors are of

importance in regard to the occurrence of the seizures. All abnormalities should be corrected if possible. Surgical removal of cerebral lesions is of value in a small percentage of the cases. Psychotherapy, regulation of hygiene and schooling or a gainful occupation are necessary in all cases. The success in the treatment of the majority of the cases, however, depends upon the ability of the physician to properly use the anti-convulsant drugs which are available. The treatment can not be standardized. All of the standard drugs should be tried. If one is not successful when used alone, it should be administered in combination with one or more of the other drugs. The most common cause of failure is the administration of inadequate dosages.

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THE PRESENT STATUS OF LIVER FUNCTION TESTS INCLUDING OBSERVATIONS ON THE NEWER FLOCCULATION PROCEDURES* †

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THE liver is an organ with many functions and a large number of tests have been devised to evaluate clinically these divers functions. A classification of the tests based on the various physiological functions of the liver described by Greene and Brugger in 1943¹ has been revised and brought up to date. This classification is presented in Table I; the more important tests according to the concept of the present authors are capitalized.

In the following pages, a brief resumé of the present status of some of these liver function tests will be presented. In the strict sense of the term, the determination of serum bilirubin or of urine urobilinogen is not a test for evaluating the functional capacity of the liver but these laboratory procedures are included in this discussion because of their importance in the diagnosis of liver and biliary tract disease.

Bilirubin in the Serum: The most accurate index of jaundice is the quantitative measurement of bilirubin in the serum. Normal values using the method of Thannhauser and Andersen² (or any of its modifications) do not exceed 1.0 mg. per cent. The method of Malloy and Evelyn³ utilizing a photo-electric colorimeter has a normal range not exceeding 0.8 mg. per cent. Recently, Ducci and Watson⁴ recommended the determination of the prompt direct reacting bilirubin; normal values are not in excess of 0.2 mg. per cent.

Bilirubin in the Urine: During an epidemic of infectious hepatitis

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† The contents of this paper were included in a lecture entitled "Interpretation of Some Important Laboratory Tests in Clinical Medicine" given by the senior author in the Friday Afternoon Series at The New York Academy of Medicine, April 16, 1948.

in the recent World War, Gellis and Stokes⁵ utilized a modified methylene blue test to detect bilirubin in the urine. They found this procedure of value in the pre-icteric stage of infectious hepatitis. The test is simple to perform and may be used as a screen in the early detection of hepatic involvement as a result of exposure to certain industrial poisons. The reliability of the methylene blue reaction, however, has been questioned⁶ since the test is not specific for bilirubin; yellow urines from normal persons and yellow substances such as potassium dichromate or ferric chloride will produce a green color when added to methylene blue.⁷ The Harrison spot test⁸ and the barium strip modification⁹ may also be used to detect bilirubinuria and, for the most part, these procedures have replaced the older tests such as those of Rosenbach, Gmelin, etc.

Icterus Index: This does not have the specificity of the quantitative bilirubin since it merely measures the intensity of yellow color in the serum as compared with an arbitrary standard. The standard most commonly used is the color of a 1:50,000 solution of potassium dichromate. Any substance that will impart yellow color to the serum will elevate the icterus index. Thus, increased amounts of carotene, nicotinic acid, riboflavin and traces of hemoglobin may give false readings. Lipemic sera are also difficult to read and give false values. As a rough clinical guide, the icterus index has its place, but in cases where the presence or absence of jaundice is in doubt, the quantitative serum bilirubin is the test of choice.

Van Den Bergh Reaction: This color reaction forms the basis for the determination of quantitative serum bilirubin. The indirect and direct van den Bergh reactions do not differentiate between hepatocellular and obstructive jaundice since both reactions are present in these disorders. In the differential diagnosis of jaundice, its main value lies in the detection of hemolytic icterus since in this type of jaundice only an indirect reaction is obtained.

The form in which bilirubin exists in the blood stream probably accounts for the type of response obtained. Bilirubinglobin derived from the breakdown of hemoglobin in the cells of the reticulo-endothelial system gives the indirect reaction whereas bilirubin resulting from the breakdown of bilirubinglobin in the parenchymal cells of the liver produces the direct reaction. It follows, therefore, that a direct van den Bergh reaction is obtained in both hepatocellular and ob-

structive jaundice since in either condition bilirubin is regurgitated into the blood stream. The positive indirect response obtained in these disorders is due to the normal amount of circulating bilirubinglobin. In hemolytic icterus, there is no regurgitation of bilirubin but an excess of bilirubinglobin is present in the blood, hence a strongly positive indirect reaction alone is obtained.

Urobilin and Urobilinogen in Urine: Urobilinogen is formed in the small intestine by bacterial reduction of bilirubin. Part is excreted in the feces while the remainder is re-absorbed into the blood stream. The major part of this fraction is returned to the liver for re-excretion, while the rest is eliminated by the kidneys. It follows, therefore, that bile must enter the small bowel for urobilinogen to be produced. In complete obstruction of the extrahepatic type, there is a persistent absence of urobilinogen in the urine. In incomplete extrahepatic obstruction, the urinary urobilinogen varies between very low to normal or slightly above normal values. In hepatocellular jaundice, the urinary urobilinogen is low or absent in the acute phase followed by a gradual increase even above normal during recovery. This late increase is due to the inability of the liver to re-excrete that portion of urobilinogen which is returned to it via the enterohepatic circulation. In jaundice due to cholangiolitis, the urine urobilinogen may be absent in the early stages; thereafter, the values tend to be within normal limits. In our hands, the modified 2-hour test as described by Watson¹⁰ has proved to be a satisfactory procedure for the quantitative estimation of urobilinogen in the urine. It should be emphasized that serial determinations of urinary urobilinogen are frequently necessary to establish the presence or absence of bile in the gastro-intestinal tract.

Bromsulphalein Excretion: Several dyes have been used clinically to test the excretory functional capacity of the liver. Of these, bromsulphalein¹¹ has won the widest acceptance. It is a sensitive and safe procedure with the added advantage of simplicity. The dye is removed from the blood stream by the Kupffer cells of the liver and then excreted by the parenchymal cells into the bile. Five milligrams of dye per kilogram of body weight is the usual dose given. Specimens of blood are then taken at 30 minutes and 60 minutes as recommended by O'Leary, Greene and Rowntree,¹² or a single specimen at 45 minutes as recommended by Mateer.¹³ Using the latter, a normal liver should clear all the dye in 45 minutes so that none remains in the

serum. Values up to 4 per cent retention are considered normal if a photo-electric colorimeter is used instead of the usual comparator block. This test, however, is of very limited value in the presence of jaundice.

Galactose Tolerance: This test, introduced by Bauer,¹⁴ is the one of choice in estimating the carbohydrate function of the liver. Unlike glucose, it does not require insulin for its metabolism and so far as is known, has no renal threshold. It has the added advantage of being rapidly absorbed. In the oral test, 40 grams of galactose dissolved in 400 ml. of water are taken with the subject in a fasting state, the urine collected for 5 hours and a quantitative estimation for urine sugar done. Normally, no more than 3 grams of sugar are excreted in the 5 hour period. The presence of impaired renal function introduces considerable error.

The galactose tolerance test is positive in acute and chronic parenchymal disease of the liver. It may be used in the presence of jaundice as an aid in differentiating parenchymal and obstructive jaundice. Bensley¹⁵ reported a positive oral galactose test in 474 cases of toxic and infectious jaundice; in 210 cases of obstructive jaundice, the test was positive in 19 per cent of cases.

Bassett, Althausen and Coltrin¹⁶ have developed an intravenous galactose tolerance test. In our opinion, the simpler oral test provides as much information as can be derived from the more complicated intravenous procedure.

Total Cholesterol and Cholesterol Partition: The value for total cholesterol in the blood plasma of normal adults varies between 160 and 230 mg. per cent. The cholesterol esters vary between 60 and 120 mg. per cent. The ratio of the combined to the total cholesterol is relatively constant ranging between 40 and 52 per cent when the Bloor¹⁷ or modified Bloor techniques are used.

Thannhauser and Schaber,¹⁸ Epstein and Greenspan,¹⁹ Hurxthal and Hunt,²⁰ Klein²¹ and Greene, Hotz and Leahy²² have shown that in the presence of severe parenchymal damage to the liver, the cholesterol esters in the blood were reduced or entirely absent. Moreover, these workers noted that a reduction of cholesterol esters was seen more frequently in parenchymatous than in obstructive jaundice, this decrease being a better indication of the severity of the damage than as an aid in differential diagnosis.

Elevation of the total plasma or serum cholesterol occurs in obstructive jaundice of both the intrahepatic (cholangiolitic) and extrahepatic types. In most instances, the total cholesterol remains unchanged in the parenchymal forms of jaundice.

Serum Albumin: Since albumin is formed exclusively in the liver, it is not surprising that the concentration of this protein fraction in the blood is decreased in certain forms of liver disease. The normal level of serum albumin is 4 to 5 gm. per 100 ml. Tumen and Bockus²³ found that a reduction in albumin was the most consistent alteration in the serum proteins in patients with chronic advanced liver disease. Lowering of the albumin-globulin ratio was not found to be as significant or as constant as the reduction in serum albumin. Post and Patek²⁴ noted a rise in serum albumin during clinical improvement in patients with cirrhosis of the liver. Persistently low or decreasing serum albumin concentration was a poor prognostic sign.

Flocculation Tests: The flocculation tests are not strictly liver function tests. These procedures determine qualitative and quantitative alterations of various fractions of the serum proteins which result from disturbed activity of the parenchymal cells of the liver.

Cephalin-Cholesterol Flocculation: This test was proposed by Hanger in 1938.²⁵ He showed that in patients with active parenchymal disease of the liver, the serum flocculated a cephalin-cholesterol emulsion. Since then, many studies have confirmed this. Positive cephalin-cholesterol flocculation has also been reported in new-born infants with jaundice,²⁶ in cases of hyperthyroidism,²⁷ malaria,²⁸ in catatonics and schizophrenics²⁹ and in many other clinical disorders.

It is believed that gamma globulin is the protein fraction that takes an active part in the flocculation of the cephalin-cholesterol emulsion.³⁰ Under normal circumstances, the serum albumin has the capacity to inhibit the flocculating action of gamma globulin. In cases of parenchymal liver disease, the serum albumin fraction has a decreased capacity to inhibit this flocculating action on the part of the gamma globulin.³¹ Readings of 2+ to 4+ are considered abnormal.

Thymol Turbidity and Flocculation: In 1944, Maclagan³² described a new test of liver dysfunction utilizing a saturated aqueous solution of thymol buffered with barbitol and sodium barbitol at a pH of 7.8. He obtained essentially the same results with this thymol solution as with colloidal gold solution; in favor of the former was the ease with

which the solution could be prepared. Subsequent work confirmed the value of the thymol turbidity test as an indicator of abnormal activity of the liver parenchyma. The mechanism, however, is unlike that of the cephalin-cholesterol flocculation test.^{33,34} Kunkel and Hoagland³⁵ showed that the turbidity of the thymol solution produced by certain sera depended on the presence of lipids and some abnormal lipo-protein associated with the beta globulin fraction of the serum. The gamma globulin fraction of the serum also played a role in the reaction. The relative importance of the different components in the reaction varied with different sera. As a general rule, in acute hepatitis cephalin-cholesterol flocculation becomes positive earlier than the thymol turbidity test while the latter remains positive longer during convalescence. Due to this fact and in view of the different underlying mechanisms, the thymol turbidity and cephalin-cholesterol tests supplement rather than supplant each other.³⁶

Methods for quantitatively determining the degree of thymol turbidity produced by sera using various photo-electric colorimeters have been reported.^{37,38} However, the original method reported by MacLagan, utilizing the formazin standards devised by Kingsbury and associates,³⁹ provides a simple and clinically accurate method. By this procedure, normal readings are 0 to 4 units.

In his original description of the thymol turbidity test, MacLagan stated that when the test was positive, flocculation frequently occurred in the tubes allowed to stand overnight; he felt, however, that this was not an essential part of the test. Neefe⁴⁰ noted that thymol flocculation remained positive for some time after the thymol turbidity reaction had returned to the normal range. In addition to supplementing and possibly increasing the sensitivity of the thymol turbidity test, the presence of 2+ to 4+ flocculation at 18 hours or its absence may aid in evaluating the significance of borderline or weakly positive thymol turbidity readings.

Colloidal Red Test: Ducci⁴¹ has recently recommended this procedure in which a colloidal suspension of scarlet red is used. The test is performed in the same manner as MacLagan's colloidal gold reaction. It is a sensitive and simple procedure and appears to parallel the cephalin-cholesterol flocculation and thymol turbidity tests. Positive flocculations probably depend on alterations in the serum gamma globulin fraction.

Zinc Sulphate Precipitations: Kunkel⁴² reported that when serum with abnormally high gamma globulin concentration was diluted with a solution containing a small amount of zinc sulphate, a turbid precipitate formed and the optical density of the suspension was proportional to the concentration of gamma globulin. Normal serum did not flocculate for at least 12 hours while serum from patients with even slight elevation of gamma globulin fraction usually flocculated within 4 hours. While the test was not specific and was positive in cases having hypergammaglobulinemia from causes other than liver disease, it was found useful in determining the alterations in gamma globulin during the course of infectious hepatitis. Kunkel stated that the test was of particular value in detecting persistent liver disease following infectious hepatitis. In a group of 41 patients with cirrhosis of the liver, the reaction was positive in each case.

Prothrombin Time: The production of prothrombin by the liver is dependent upon ingested vitamin K. Bile salts are necessary for the absorption of vitamin K from the small bowel. In liver disease, the ability of the parenchymal cells to produce prothrombin may be impaired thus resulting in a disturbance in blood coagulation. Various methods are available for determining prothrombin time; in our hands, the Link-Shapiro^{43,44,45} modification of the Quick method has proved most satisfactory. With this procedure the normal prothrombin time is 14 to 16 seconds for the undiluted plasma and 36 to 45 seconds for diluted (1:8) plasma.*

The response of the prothrombin time to the parenteral administration of synthetic vitamin K often offers aid in differentiating between hepatogenous and extrahepatic obstructive jaundice.⁴⁶ In the early stages of the latter, there is no impairment on the part of the liver cell to produce prothrombin. The increased prothrombin time is due to the impaired absorption of vitamin K resulting from a total absence or diminution of bile salts entering the duodenum. Thus, the parenteral administration of vitamin K leads to the restoration of normal prothrombin values in over 85 per cent of such cases. In patients where the jaundice is due to damage of the parenchymal liver cells, this restoration does not occur following the injection of vitamin K.

Hippuric Acid Synthesis: Hippuric acid synthesis in man occurs in the liver by the union of the benzoate radical with glycine. When 6

* These values vary with the type of thromboplastin used. In this institution, thromboplastin manufactured by the Maltine Company, New York, is employed.

gm. of sodium benzoate is given orally, the normal liver can produce 2.5 to 3 gm. of hippuric acid within 4 hours.⁴⁷ The excretion of less than 2.5 gm. of hippuric acid in the urine in 4 hours signifies liver damage providing, of course, that renal function is not impaired.

The test may be made more sensitive by giving the sodium benzoate intravenously.⁴⁸ In this instance 1.77 gm. of sodium benzoate in 20 ml. sterile water is slowly injected intravenously. One hour later, the patient voids and the hippuric acid concentration in the urine is determined. The normal range is 0.7 to 0.95 gm. of hippuric acid.

Hippuric acid synthesis by the liver is reduced in acute and chronic parenchymal disease and in metastatic carcinoma of the liver. It is normal in obstructive jaundice provided no secondary biliary cirrhosis has resulted from longstanding obstruction.

Serum Alkaline Phosphatase: Alkaline phosphatase is an enzyme concerned with several metabolic processes. Whether the liver produces alkaline phosphatase has not been definitely established; however, this enzyme is present in the bile. In cases of obstructive jaundice (intrahepatic and extrahepatic), the serum alkaline phosphatase is elevated. Normal values for adults by the Bodansky^{49,50} method range from 4 to 6 units per 100 ml. of serum. An alkaline phosphatase above 13 units in an adult with jaundice is indicative of an obstructive lesion. It must be remembered that many other clinical entities may cause an elevation of the serum alkaline phosphatase, e.g., hyperparathyroidism, Paget's disease of bone, metastatic carcinoma to bone, etc. When properly evaluated, however, the serum alkaline phosphatase is a definite aid in the differential diagnosis of jaundice.

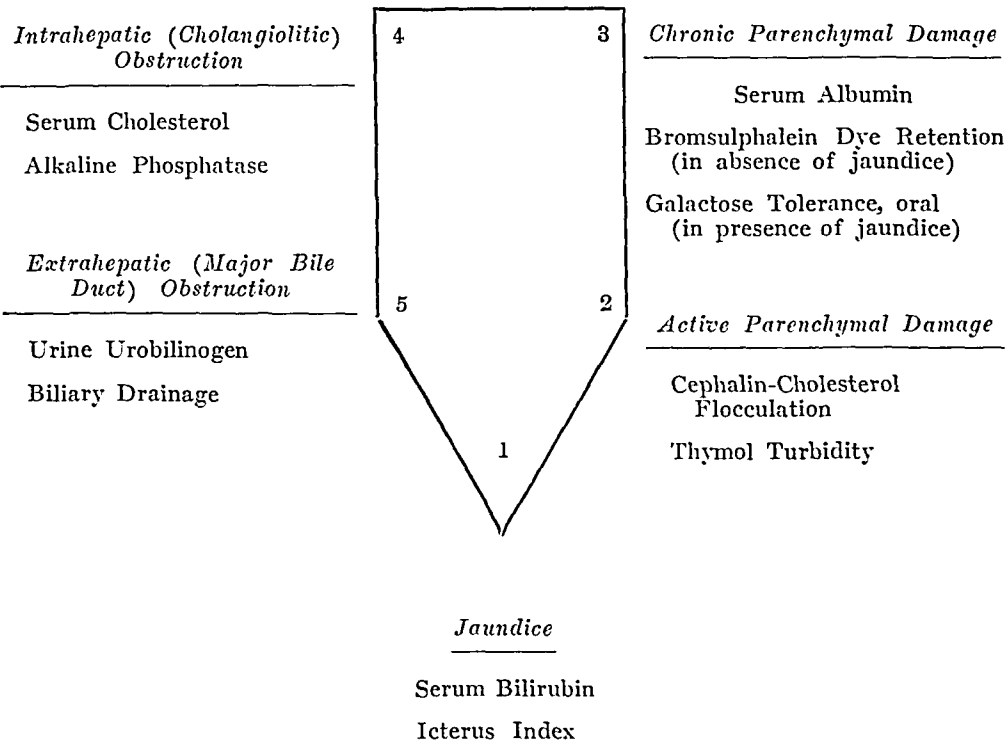
DISCUSSION

The clinician is frequently overwhelmed by the large number of tests available for the estimation of liver function. A perusal of Table I exemplifies this state of affairs. For this reason, there is presented in Figure 1 a simple schema (modified after Greene⁵¹) coordinating the more important tests for estimating the functional capacity of the liver and for differentiating the various types of jaundice.

In this figure, liver and/or biliary tract disease is analyzed according to the presence or absence of five factors, namely, jaundice, active (acute) parenchymal damage, chronic parenchymal damage, intrahepatic obstruction and extrahepatic obstruction. The present authors

FIGURE 1.

SCHEMA FOR COORDINATION OF LIVER FUNCTION TESTS
(MODIFIED AFTER GREENE)



Types of Liver Disease

Alteration in Pattern

Hemolytic Icterus	1
Acute Hepatitis	1, 2
Cirrhosis of Liver with Jaundice	1, 2, 3
Cirrhosis of Liver without Jaundice	2, 3
Cholangiolitic Obstruction	1, 2, 4
Common Duct Obstruction	1, 4, 5
Common Duct Obstruction with Biliary Cirrhosis	1, 2, 3, 4, 5
Carcinoma of Liver (Primary or Secondary)	Irregular

have grouped these factors around a porphyrin ring because of the five points available in this configuration (peculiarly enough, the basic structure of bilirubin is a porphyrin ring). Thus, the presence of jaundice may be revealed by an elevation of the serum bilirubin and icterus index, active parenchymal damage by positive cephalin-cholesterol flocculation and thymol turbidity tests, chronic parenchymal damage by decreased serum albumin, by bromsulphalein dye retention in the absence of jaundice and by an abnormal galactose tolerance test in the presence of jaundice, intrahepatic (cholangiolitic) obstruction by an elevated serum cholesterol and alkaline phosphatase and finally, extrahepatic (major bile duct) obstruction by the persistent absence of urobilinogen in the urine and of bile in duodenal drainage. Below the figure, various types of liver disease are tabulated and the associated alterations in the pattern are indicated. Thus, in hemolytic icterus, there is jaundice as revealed by a high serum bilirubin and icterus index but no disturbances in the other four factors. In cirrhosis of the liver without jaundice only factors 2 and 3 are abnormal, namely, evidence of active parenchymal damage (positive flocculation tests) and chronic parenchymal damage (decreased serum albumin and bromsulphalein dye retention) and so on.

This schema is by no means complete or infallible. It is intended as a framework to which may be added other liver function tests depending upon the particular desires or experiences of the clinician. It possesses, however, simplicity and not infrequently affords diagnostic aid by the utilization of relatively few laboratory procedures.

Under the heading of flocculation tests, a number of procedures have been described which attempt to assay aberrations of the serum protein fractions resulting from disease of the parenchymal cells of the liver. In Table II the results obtained in five patients chosen from a large series⁵² are detailed. Thus, in Case 2, a patient with infectious hepatitis, it may be noted that each of the flocculation or precipitation tests is abnormal. Case 3 is an example of the results obtained in early obstructive jaundice; each of the flocculation tests remains normal even in the presence of marked hyperbilirubinemia. When secondary biliary cirrhosis supervenes during the course of obstructive jaundice, the flocculation procedures become abnormal as may be noted in Case 4. The findings in active portal cirrhosis are shown by the results obtained in Case 5; hepatic damage is revealed by abnormal flocculation tests

TABLE II. COMPARISON OF SEVERAL FLOCCULATION TESTS IN PATIENTS WITH HEPATIC DISEASE

<i>Case</i>	<i>Diagnosis</i>	<i>Icterus Index units</i>	<i>Cephalin-Cholesterol Flocculation 24 hour reading</i>	<i>Thymol Turbidity units</i>	<i>Colloid-al Red Flocculation</i>	<i>Zinc Sulphate Precipitation hours</i>				
		4—6	0—+	0—4	0—+	0—2	0	0	0	0
1	Normal	6	±	1	0	0	0	0	0	0
2	Infectious Hepatitis	176	++++	12	++++	5	++	++++	++++	++++
3	Obstructive Jaundice Due to Carcinoma of the Head of the Pancreas	121	0	1	0	0	0	0	0	0
4	Congenital Atresia of the Common Bile Duct with Secondary Biliary Cirrhosis	140	++	5	+++	4	0	+	++	+++
5	Portal Cirrhosis	24	++	5	+	5	+++	++++	++++	++++
6	Familial Hepatic Dysfunction	12	+++	2	++	3	0	+	++	+++

throughout. In Case 6, a slight dissociation between the various procedures is demonstrated. In this patient with familial hepatic dysfunction, the thymol turbidity test alone remains normal; it may be assumed that the serum lipoproteins were not affected by the underlying hepatic dysfunction.

It appears worthwhile to stress again here that these simple though important laboratory procedures supplement each other. When these flocculation tests are carried out simultaneously, a better panorama of the alteration in the serum protein fractions is envisaged than can possibly be obtained by the performance of any single procedure alone.

SUMMARY

1. A review and discussion of the practical liver function tests available to-day are presented.
2. The newer flocculation tests are described and compared.
3. A simple schema is presented coördinating several liver function tests as an aid in the diagnosis of diseases of the liver and biliary tract.

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REVIEW OF STUDIES ON BLOOD SUGAR*

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DR. MOSENTHAL and Members of the New York Diabetes Association, I thank you for your words of encouragement. This title, of course, permits a good deal of latitude to the lecturer, and what applies to the lecturer will also apply to the discussers who are to follow.

By way of introduction I should like to quote von Noorden's views on Diabetes Mellitus, as published at the beginning of this century in Volume III of his "Metabolism and Practical Medicine."¹

"So long as we know no more about the nature of the diabetic process than we do at present we must, in common with former generations, define diabetes mellitus in terms of its most important clinical symptom—as a chronic disease in which grape-sugar is excreted in the urine. This definition however needs certain limitations, of which the following may be mentioned:

1. The quantity of sugar must be demonstrable by the ordinary clinical tests. The question whether normal urine contains traces of grape-sugar, to be detected only by the most delicate methods, may be left for the moment.

2. The grape-sugar must occur in the urine when the carbohydrate in the food is not more than that in ordinary human diet, or when the carbohydrate food is reduced in quantity or even stopped altogether. Cases where glycosuria only occurs after partaking of unusually large quantities of carbohydrate can scarcely be regarded as diabetes mellitus in a clinical sense.

3. The tendency to glycosuria must be persistent—that is to say, it must last at least some weeks or months. There are many conditions of ill-health in which a temporary disposition to glycosuria occurs. Such are not called diabetes mellitus, although there is considerable evidence that in both cases the glycosuria has the same fundamental

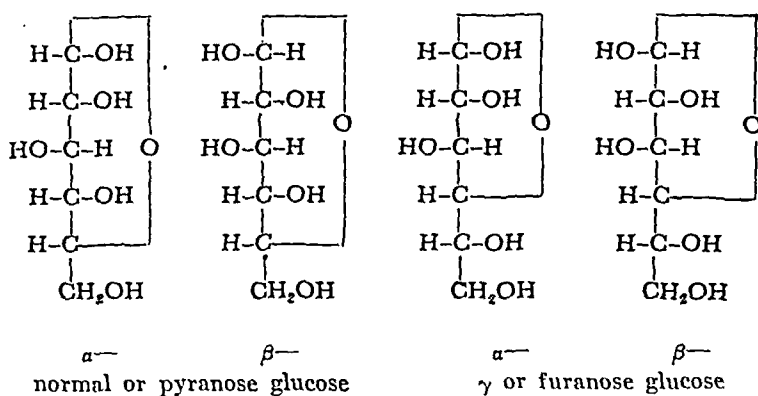
* Presented March 19, 1948 at an Open Meeting of the New York Diabetes Association at The New York Academy of Medicine.

cause (see anomalies of pancreatic function)."

I would draw attention to one point only, namely, the stress given to the estimation of sugar in the urine. Since that time emphasis has shifted from the estimation of sugar in urine to that in blood. I should now like to quote from Dr. Best's account of the "Discovery of Insulin" as narrated to the American Diabetes Association at the 25th Anniversary celebrations of its discovery. "It is obvious to all of you that we had many advantages over our predecessors in the search for the antidiabetic hormone. Certainly one of the greatest—probably the most important of all—was the availability of a good method for the estimation of sugar in small amounts of blood." It is with good methods for the estimation of sugar in small amounts of blood, and some results drawn from them that we are now concerned. No other constituent of the tissues is tested for as often as sugar. Yet no one has seen sugar from blood, for it has never been isolated as such. In 1892 Pickard is reported to have prepared from blood an osazone, which appeared to be identical with glucosazone. It would not seem to be a difficult matter to obtain a crystalline preparation of the sugar of the blood in reasonably quantitative yield. As far as I am aware it has not however been done. In spite of the lack of this direct and most satisfying of all proofs, there is a great deal of evidence supporting our general belief that the sugar of the blood is an equilibrium mixture of α — and β — glucose of the normal or pyranose type. In the fasting state we may say that it and it alone, in free solution, constitutes the uncombined sugar of the blood. In the cells there is a very small quantity of sugar phosphates; the amounts are always small. There is also present in blood plasma a relatively large amount of sugar of one kind and another, in the form of polysaccharides, conjugated with, and an integral part of the various globulin proteins. With such sugar constituents we are not concerned, though this combined sugar has been the subject of many scientific treatises. What we are concerned with is the freely diffusible reducing sugar of the blood, which under some conditions remains surprisingly constant in amount and yet at other times will vary in amount rapidly and widely.

Glucose is a reducing sugar and since it contains within its molecule asymmetric carbon atoms it is optically active; that is, its solutions rotate the plane of polarized light. At one time because the reduction value and the optical rotation value of a blood filtrate did not show

FIGURE 1



corresponding agreement, and because the optical rotation was lower than the equivalent reduction value, if the material being estimated was normal glucose it was supposed that some of the sugar existed in another form, α — and β —, γ — glucose. As can be seen in Figure 1, the α — and β — forms of γ glucose are represented as having a smaller ring structure than the corresponding forms of normal or pyranose glucose. This γ glucose has a lower specific rotation, and will reduce Fehling's solution rapidly even at room temperature and is therefore sometimes referred to as "reactive glucose." It was therefore seized on by some as the biologically active form of glucose. We now know, that the earlier evidence for such a reactive form of glucose was not valid because the various biological extracts, that of blood included, which were examined contained other substances besides sugar possessing both reducing and optical properties. There is, of course, nothing mysterious about this reactive form of the simple sugars. It is the reactive form of fructose (or laevulose) that is present in ordinary cane sugar, a fact that foiled chemists for years in their efforts to synthesize cane sugar. Fructose phosphates, to which reference will be made later, also have this smaller ring structure. There is no evidence, nor is there any need at present, to suppose that glucose is metabolized via "reactive" or γ glucose. It is now realized that the relatively inert glucose molecule becomes more active metabolically when esterified with phosphoric acid.

There are a variety of methods for the estimation of glucose in blood. The blood is first deproteinized, by one of a number of protein precipitants. The popular methods on this continent depend upon the

estimation of the sugar in the filtrate by heating under specified conditions with a copper solution. These copper solutions might all be regarded as modifications, some of them very considerable modifications, of the well known and prototype solution of Fehling, which will be celebrating its centennial next year.

Copper sulphate is a common constituent, but the other ingredients vary in identity and in amount. In general it might be said that those who have designed such modifications have had these objects in mind: firstly, a solution which will give the greatest reduction per unit of glucose, and secondly, the smallest reduction for those other constituents of blood filtrates which are also reducing agents. There are just two other points which should be mentioned here: firstly, with these various copper reagents and indeed with most other reagents used for the estimation of blood sugar there is no theoretical amount of reduction which should be made per unit of glucose present, i.e., one cannot calculate the amount of cuprous oxide formed by a known amount of glucose. This is so because the end aldehyde group of the sugar is not the only reducing grouping, since in the alkaline solution the glucose molecule split at a number of points and some of these split products are themselves reducing. It is therefore necessary to bear in mind the empirical nature of these estimations and the prime necessity of carrying out each estimation under the prescribed conditions. There should be strict comparison with the behavior of standard solutions of glucose of comparable concentration treated in precisely the same way. Some methods are not very reliable when glucose is present in low concentration. Secondly, a copper reagent designed by one investigator will not necessarily give the same reducing value with all kinds of blood filtrate. That is to say, different deproteinizing reagents give precipitates which carry down with them varying quantities of non-sugar reducing substances. The copper reagents purporting to give free sugar values should therefore be used with the particular kind of blood filtrate for which they were designed.

It is sometimes argued (sometimes, one suspects, just for the sake of argument!) that these so-called "true glucose" methods for blood, claim to be so because they give lower values than the older methods. This attitude gives rise to the expression "the so-called true blood sugar concentration. . . ." The imputation is that the lower the reduction value the more likely the designer or analyst is to call his method one for the

TABLE I. HIGH VALUES FOR NONGLUCOSE REDUCING SUBSTANCES IN A SUGAR TOLERANCE TEST

Timing	<i>Venous Blood Sugar, Mg. per 100 cc., True Blood Sugar</i>	<i>Venous Blood Sugar, Mg. per 100 cc., Folin-Wu Method</i>	<i>Nonglucose Reducing Substances, Mg. per 100 cc.</i>
Fasting _____	87	138	51
100 Gm. glucose by mouth _____			
½ hour later _____	102	176	74
1 hour later _____	109	178	69
2 hours later _____	90	168	78

According to the true venous blood sugar this is a normal curve, while the Folin-Wu method indicates a diminished sugar tolerance. This is an example of the hazard of an erroneous interpretation of blood sugars when the analyses include nonfermentable substances, whereas the correct diagnosis is revealed by the true blood sugar determinations.

Male (S. B. G.) age 44. Glycosuria found on Life Insurance examination 7-8 years ago; no glycosuria since that time. [Mosenthal and Barry (1946)]

estimation of true blood sugar, and the critic suspects that something has happened to the sugar, either it is lost in the protein precipitate or there is something in the filtrate or the sugar reagent which prevents the full reducing activity of the glucose. This is not necessarily so. The criteria which should be obeyed were those laid down very clearly by Benedict (1928).² Our techniques have improved but the criteria are essentially unchanged. The blood filtrate, after rapid fermentation with a relatively large amount of well-washed yeast, should give very little or no reduction with the reagent. The reduction, that is the glucose value obtained with the unfermented filtrate should not be less than the value obtained as the difference between total reduction before fermentation and residual reduction after fermentation by another standardized method. And lastly, the glucose added in known amount to the fermented filtrate should give the calculated reduction.

The titrimetric copper methods have been modified so that they may be turned into colorimetric procedures; as for example that of Nelson (1944)³ and of Somogyi (1945).⁴ In the clinical laboratory one method may be more convenient than another. But surely every effort should be made to use a method in which non-sugar reducing substances

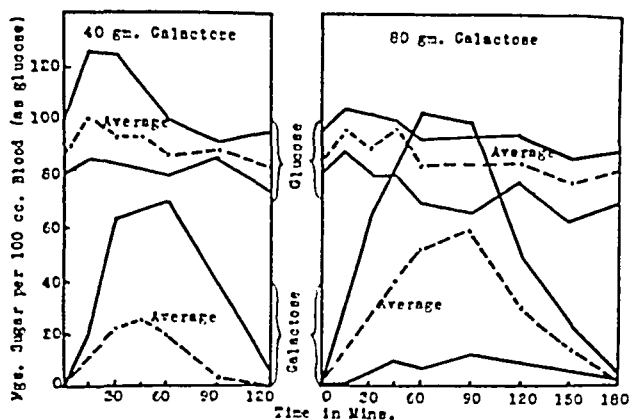


FIG. 2. Maximal, average, and minimal blood sugars after the ingestion of 40 gm. of galactose and 80 gm. of galactose. Average urine galactose after 40 gm. = 500 mg. Average urine galactose after 80 gm. = 2650 mg. [Harding and Grant (1933)]

play little or no part. It is claimed with other methods in current use that while these non-sugar reducing substances give a substantial figure when calculated in terms of glucose, this value is relatively constant in different individuals in the absence of renal disease and that there is little variation in the same individual during the course of a glucose tolerance test. In the experiences of some, these assumptions are not justifiable, e.g. in Table I are shown results obtained by Mosenthal and Barry (1946).⁵ Some clinicians state that it does not matter what method is used as long as they are told the normal limits as obtained by these methods. But I do not think this is a sound argument. If the non-sugar reducing substances vary from individual to individual and certainly if there is variation in the same individual over the course of the glucose tolerance curve, then surely a method giving true sugar values would be more reliable. It would be especially useful in cases of mild diabetes.

Mention might also be made here to the extensive work done on the "true sugar" of urine. The preliminary treatment of urine before quantitative testing for glucose was well explored by Harding and his associates (see Nicholson and Archibald⁶).

If galactose or fructose is fed alone, as is glucose in performing the oral glucose tolerance curve, there is a substantial increase in the sugar concentration of the blood.^{7,8,9} With galactose the increased concentra-

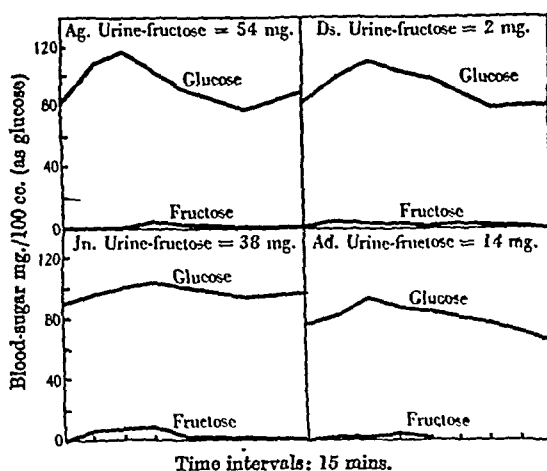


FIG. 3. Showing glucose and fructose in cutaneous blood after oral administration of 50 g. fructose. [Harding, Nicholson and Armstrong (1933)]

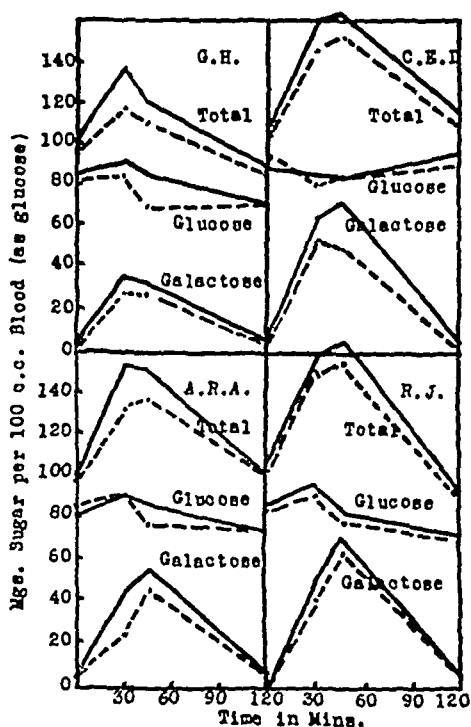


FIG. 4. Arterial-venous differences in blood sugars after the ingestion of 40 gm. of galactose. The solid line represents arterial blood; the broken line, venous blood. [Harding and Grant (1933)]

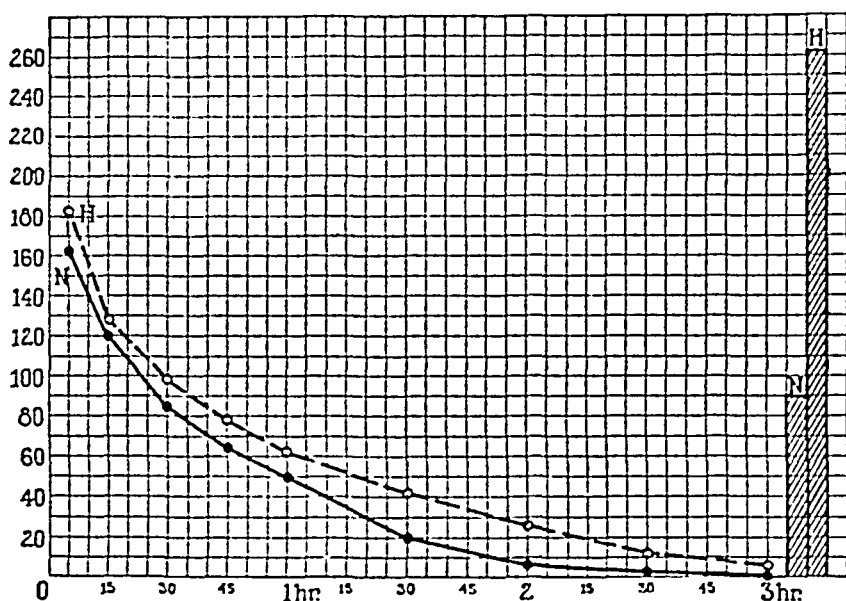


FIG. 5. Curves showing the clearance of galactose from the blood following the intravenous injection of 500 mgm. of galactose for each kilogram of body weight in the normal, *N*, and hepatectomized, *H*, dog. The curves are expressed in milligrams of galactose for each 100 cc. blood. The rectangles indicate the total amount of galactose excreted in the urine; shown as milligrams for each kilogram of body weight so that 500 would represent complete recovery of galactose. [Bollman, Mann and Power (1935)]

tion of blood sugar is largely due to the presence of galactose, and the maximum blood galactose concentration increases when increasing amounts of galactose are fed (Fig. 2). When fructose is absorbed the increase in blood sugar is largely due to an increase in glucose, the concentration of fructose being very small (Fig. 3). In the absorption of these hexoses from the small intestine it is supposed that all three are phosphorylated, and passed into the blood as free hexoses, with possibly some small amount of conversion of fructose and galactose to glucose during the absorption process.

The rate at which the galactose is removed from the blood is generally regarded as an index of the efficiency of the liver; at least as far as carbohydrate function is concerned. Galactose is of little value in the prevention of hypoglycemia in the dog following removal of its liver (Bollman, Mann and Power, 1935¹⁰). But there can be no doubt that galactose is used by tissues other than the liver (Fig. 4). Further when galactose is injected into a liverless dog the rate of removal of the galac-

tose is much the same as before removal of the liver (Fig. 5). There is a greater excretion of galactose in the urine of the liverless animal.

Recent work has shown that the kidneys can contribute to the maintenance of the concentration of blood sugar; while the liver must not therefore be regarded as the sole source of the blood sugar, it is easily the prime source, in quantity. The approximate amount produced under resting conditions may be gauged from studies on hepatectomised animals. The liverless dog requires about $\frac{1}{4}$ g./K./hr. to maintain a normal blood sugar level. For a variety of reasons the amount of sugar secreted by the liver ordinarily may be appreciably less than this. I should like to comment upon one piece of evidence only. It was shown that the oxygen consumption of the liverless dog is the same as before removal of the liver (Mann and Boothby, 1928¹¹), and substantially the same results were obtained by Drury and McMaster¹² with the liverless rabbit. Bearing in mind the considerable metabolic activity of the liver, it is not easy to account for this lack of a decrease in oxygen consumption. It is possible that after the operation there is increased tone in the muscles: that is, the liverless animal is not really in the basal state. One is therefore led to the conclusion that the rate of usage of sugar by the peripheral tissues of the liverless animal is higher than that ordinarily provided by the liver in the resting animal. Crandall and Cherry by means of London cannulae suggest that the amount may be about 180 mgm./K./hr. for the normal dog.¹³

There can be no doubt that in the disposal of sugars absorbed from the small intestine or injected parenterally the liver plays an important part. The shape of the glucose tolerance curve and for that matter the fructose or the galactose tolerance curves are partly determined by the activity of the liver. It comes as something of a surprise to learn that the glucose and the galactose tolerance curves are so little altered in the liverless animal. Thus the intravenous injection of $\frac{1}{2}$ g. per kilo body weight of galactose or of glucose in the liverless dog gives essentially the same die-away curves as in the intact animal. And yet it is well established clinically that the glucose tolerance curve is sometimes altered in liver disease; and that the excretion into the urine of galactose is appreciably increased in liver disease. Part of the explanation may well be that the liverless animal is not in the basal state: that is to say it is undoubtedly using more sugar (glucose or galactose) than would the peripheral tissues of the normal resting animal. This point is not

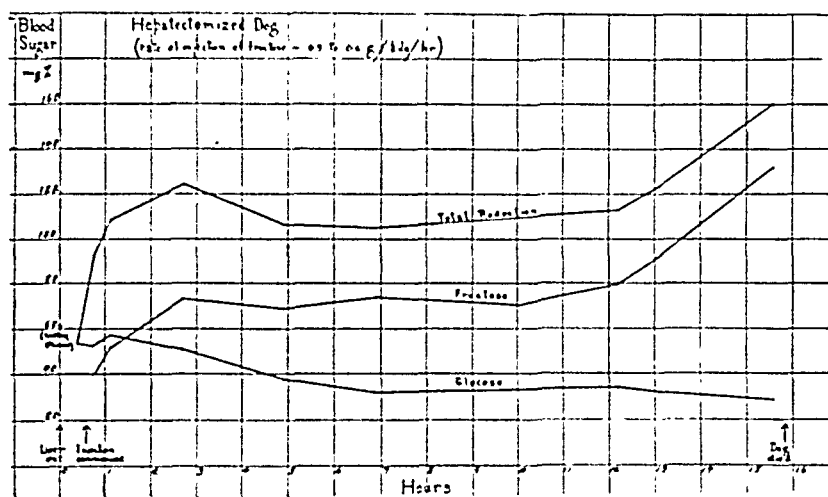


FIG. 6. [Griffiths and Waters (1936)]

generally appreciated. If it is borne in mind it will be seen that the interpretation of laboratory findings in clinical cases will be in better agreement with that of experimental work carried out on animals.

Fructose does prevent hypoglycemia in the liverless animal, but does not relieve the symptoms of hypoglycemia once established. We have found that while fructose will prevent the decrease in the blood glucose concentration of the liverless animal, there is no increase in the glucose concentration even when large doses of fructose are injected¹⁴ (Fig. 6).

There is another interesting reaction with fructose which I think again concerns the liver and may well be part of the homeostatic mechanism concerned with sugar equilibria in that organ. The intravenous injection of fructose into a dog absorbing glucose from its intestine markedly decreases the concentration of glucose in the blood. That is to say, there is a very marked effect upon the glucose tolerance curve (Fig. 7). That this is not the result of a stimulation of the pancreas to secrete extra insulin, was shown by experiments on depancreatized dogs; for the same effect of fructose on the glucose tolerance curve could be demonstrated, provided insulin (exogenous in these animals) is present in the tissues (Fig. 8). A similar effect has been obtained on injecting a solution of sorbitol, instead of fructose.

A possible interpretation of this fructose effect may be based upon

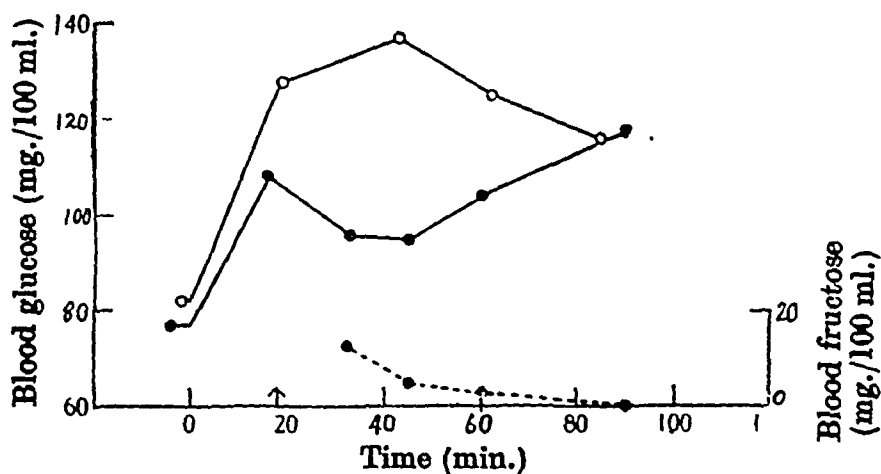


FIG. 7. The effect of fructose on the glucose tolerance curve of the normal dog.

- — ○ Glucose tolerance curve (control).
- — ● Glucose tolerance curve after intravenous injection of fructose (0.5 g. per kg. body weight) at time marked with arrow.
- - - - ● Blood fructose values.

(Arrow indicates time of sugar injection. [Fletcher and Waters (1938)])

the recent investigations of the hexokinase and related enzyme systems. It will be seen (Fig. 9) that blood glucose is converted to glucose-6-phosphate by the hexokinase acting in conjunction with adenosine triphosphate. Glucose-6-phosphate is converted to glucose-1-phosphate and this latter compound through the mediation of phosphorlyase is converted to glycogen. Fructose can also be phosphorylated by the same hexokinase system and the fructose-6-phosphate so formed can be converted to glucose-6-phosphate. From a simple view of the mass action effects one would suppose that increasing the concentration of glucose-6-phosphate from fructose-6-phosphate would decrease the amount of glucose directly esterified to glucose-6-phosphate and therefore the blood glucose instead of decreasing would rather increase in concentration. Presumably some fructose-6-phosphate is converted to glucose-6-phosphate, but some passes directly to fructose-1:6-diphosphate. Fructose-1:6-diphosphate is converted by a series of changes into lactic acid and chemical energy is liberated, especially for the resynthesis of adenine triphosphate. It may be that the availability of this compound is the limiting factor in the synthesis of glucose-6-phosphate from blood glucose. In this manner one might account for the increased rate of removal of blood glucose following the administration

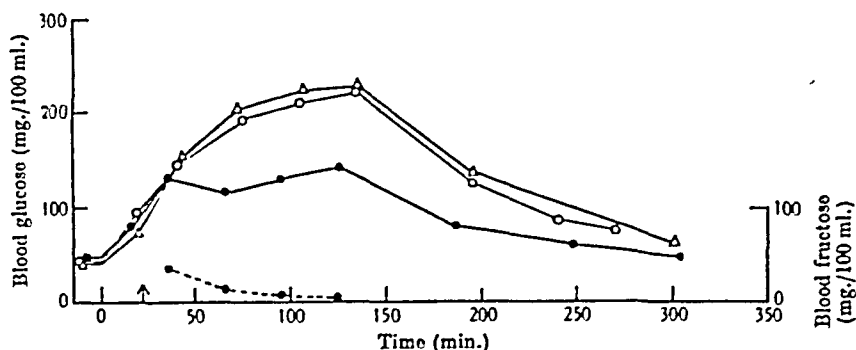


FIG. 8. The effect of fructose on the glucose tolerance curve of the depancreatized dog. Dog M. 16.3 kg. Insulin: daily 18 units, day before experiment 6 units a.m., 28 units p.m.

- Glucose tolerance curve (control).
- △—△ Glucose tolerance curve after injecting galactose (0.67 g. per kg. body weight).
- Glucose tolerance curve after injecting fructose (0.67 g. per kg. body weight).
- Blood fructose values after injecting fructose.

(Arrow indicates time of sugar injections.) [Fletcher and Waters (1938)]

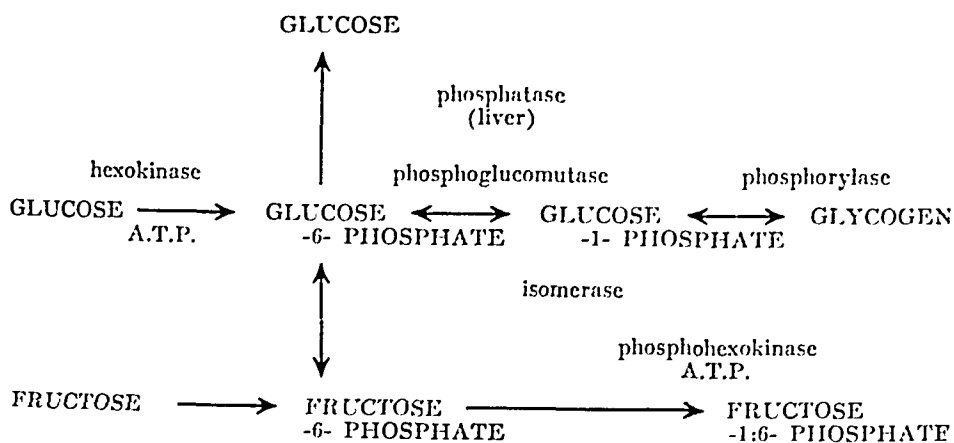


FIGURE 9

of fructose. Certainly there is evidence that fructose 1:6 diphosphate is formed, because there is an appreciable increase in blood lactic acid in animals receiving fructose.

This fructose test may have some application of clinical interest. While an injection of fructose into a normal fasting dog or into a fasting depancreatized dog with relatively low blood sugar following the administration of insulin produced no decrease in the blood glucose con-

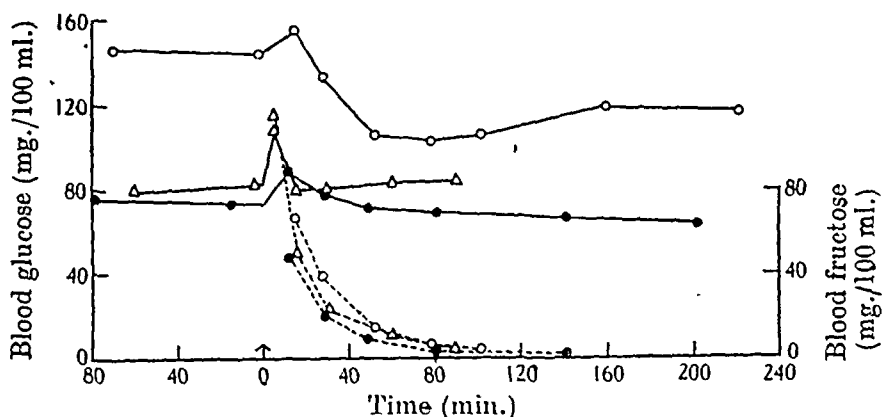


FIG. 10. The effect of fructose on the blood glucose concentration of the fasting normal dog and of the fasting depancreatized dog.

Δ—Δ	Glucose }	Fructose (0.5 g. per kg. body weight) injected into
Δ- - Δ	Fructose }	normal dog.
○—○	Glucose }	Fructose (0.67 g. per kg. body weight) injected into
○- - ○	Fructose }	fasting depancreatized dog (receiving insulin) with
		high blood sugar.
●—●	Glucose }	Fructose (0.5 g. per kg. body weight) injected into
●- - ●	Fructose }	fasting depancreatized dog (receiving insulin) with
		low blood sugar.

(Arrow indicates time of sugar injections.) [Fletcher and Waters (1938)]

centration, it was possible on two occasions to demonstrate a decrease in blood glucose in the fasting animal. On these occasions the depancreatized dogs had received protamine zinc insulin the night before, as usual, but the following morning the blood sugar was appreciably above the normal fasting level; injection of fructose into these animals produced a significant decrease in the fasting blood glucose concentration (see Fig. 10). Thus an intravenous injection of fructose into a fasting diabetic patient may lower, temporarily, the high blood glucose, or there may be an immediate increase in the blood glucose. The former reaction might be interpreted as indicating that some insulin was still being supplied by the pancreas, while the latter response might indicate an absent or very small supply of endogenous insulin. This, of course, is speculation. Certainly no such experiments have been done.

This rather curious effect of fructose which can be demonstrated in dogs may provide an explanation for earlier reports that, for a short time at least, some diabetic patients were said to be able to assimilate added fructose better than a corresponding extra quantity of glucose, as judged by the resulting glycosuria. There may be an increased synthesis of glucose to liver glycogen.

It has already been pointed out that the best known reaction of insulin, namely its lowering effect on the blood sugar, was the reaction most useful, indeed it was the indispensable test, in its isolation. The next best known reaction of insulin is on the synthesis and storage of glycogen, both in muscles and in the liver; though the role of insulin in the storage of glycogen in the liver is on occasion equivocal. Some would point to the part played by the hyperglycaemic factor, of which we shall have more to say later. However, the deposition of glycogen was the first clue as to what happened to some at least of the blood sugar under the action of insulin. There were many who made the far-reaching interpretation from this sort of experimental finding, that before glucose could be metabolised it had to be synthesised to glycogen. The evidence for this view was always circumstantial and we now know, particularly through the isotopic studies of Stetten and his associates,¹⁵ that the bulk of glucose is not transformed into glycogen. Glycogen is a storage form of glucose, and, provided there is ample blood sugar, insulin will cause increasingly large deposits of glycogen. More recently and again as a result of isotopic studies with deuterium, Stetten and Klein (1946),¹⁶ supporting and extending earlier conclusions of Drury and others, have shown that insulin causes a rapid conversion of blood glucose to fat, presumably, in the liver. Thus fat can be regarded as another form of storage of blood glucose, and indeed much more of the blood glucose of an ordinary mixed diet is stored as fat, under the action of insulin, than is stored as glycogen. We may still regard insulin as indubitably playing the role of a storage hormone: converting blood glucose above a certain concentration to fat and glycogen for later use. This storage mechanism is radically interfered with in the absence of sufficient insulin. What other role or roles insulin plays is still being vigorously investigated; such for example as the effect of insulin on oxygen consumption—is the oxygen consumption increased or is oxidation shifted from one type of metabolite to another?

It will be recalled that Boxer and Stetten (1944)¹⁷ showed that far more glycogen is formed from glucose in the previously fasting rat receiving a solution of glucose by mouth than is formed in the rat feeding in normal fashion on a high carbohydrate diet. They supposed that this difference was due to the fasting state. Now it is known that fasting tends to decrease the formation of glycogen (at least less glycogen is deposited in a rat receiving glucose previously fasted 48 hours than in

a rat fasted 24 hours.) Therefore one might suppose that the effect of fasting for 24 hours as in Stetten's experiments would be to decrease glycogen synthesis over what would occur in a well-fed rat. The explanation for the difference might reasonably be that in the case of rats fed on the high carbohydrate diet (starch) the blood sugar would not rise as high as in the rat fed glucose, and therefore less glucose would be stored as glycogen in the former animals. That is to say, the effect of insulin is to remove rather rapidly blood sugar in excess of a certain concentration, and the higher the glucose level above that concentration the more storage of glycogen will occur. Whether the much higher blood glucose concentration in rats receiving glucose only, results in an increased rate of secretion of insulin from the pancreas is still something that one might mention without being able to throw any more light on the problem. Other hormones we know play their part: a more satisfying description of what happens in this instance and in others will be obtained when further knowledge of the enzyme systems involved is elucidated and the way in which the various hormones influence these enzymic reactions.

A good deal of interest has been aroused amongst laboratory investigators recently about the hyperglycemic factor present in some preparations of insulin, both crystalline and amorphous. Whether the substance responsible for this effect is present as such in the pancreas or whether it is a product formed during the isolation of insulin has yet to be determined. If the former is the case, it would at least prove of continued interest to physiologists. The physiological significance has yet to be shown; so also has its clinical significance. It has been stated that only "novo" insulin, produced in Denmark, is consistently free of this hyperglycemic material.

Shipley and Humel (1945)¹⁸ incubated rat liver slices in the animal's own serum and noted that the glycogenolysis which occurred was increased by the addition of insulin. They also found that the rate of accumulation of new carbohydrate was increased. These effects were obtained with liver slices, possessing a high initial glycogen content, from well-fed animals. Having in mind the experiments of Bouckaert and de Duve as described in their review (1947)¹⁹ on the action of insulin, it was natural to suspect that this effect on rat liver glycogen which Shipley and Humel obtained might be attributed to the hyperglycaemic factor which Bouckaert and de Duve had shown to be

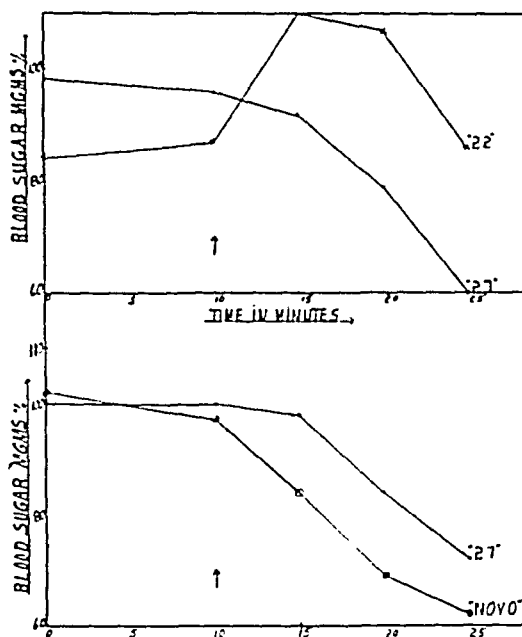


FIG. 11. Effect of insulin on fasting blood sugar. (Arrows indicate times of insulin injections.) [Balasubramanyam and Waters]

present in some insulin preparations. They were able, for example, to show that the fall in the blood sugar concentration of a rabbit injected with 30 units of insulin, free of the hyperglycaemic factor, could be prevented either by an infusion of glucose at the high rate of 1.4 g./k./hr. or by an infusion of about 20 u./k./hr. of another brand of regular insulin. I therefore decided, with Mr. G. Balasubramanyam of Madras, India, at present a postgraduate student in Dr. Best's laboratories, to investigate more closely this effect of insulin on the glycogen of rat liver slices. These experiments are still in progress; the conclusions we draw from them will therefore be somewhat speculative and will await confirmation by further tests which we are now carrying out. Our plan was to use two samples of crystalline insulin, of different potency but manufactured by the same pharmaceutical house. We are greatly indebted to Mr. A. H. Lacey of the Insulin Committee Laboratory at the University of Toronto for these two assayed samples of insulin. One sample assayed at 22 units per mgm. the other at 27 units per mgm. We presumed that the insulin of lower potency would con-

tain more of the hyperglycaemic factor. Solutions of these two preparations were therefore injected intravenously into fasting rabbits in amount equal to 1 unit per kilo body weight and it was soon apparent that the less potent insulin preparation did give a definite preliminary hyperglycaemia, while the more potent preparation gave only a slight hyperglycaemic effect. Indeed, it would be truer to say that, whereas a sample of "novo" insulin, of Danish origin, known to be free of hyperglycaemic material caused an immediate decrease in the blood sugar of the fasting rabbit, our more potent preparation—the one assaying at 27 units per mgm.—did not cause hyperglycaemia but rather showed a lag in its production of hypoglycaemia (Fig. 11).

The effect of the two insulin samples, which for convenience we have called insulin 22 and insulin 27, was also obtained on rat liver slices from well-fed animals. Three slices of liver, each of about 50 mgm. weight and about 0.3 mm. thickness, were placed in three Warburg vessels, each containing 1 cc. of the rat's serum. The first slice was the control. To the second slice 2 units of 27 insulin were added and to the third slice 2 units of 22 insulin. The vessels were gassed with a mixture of 95 per cent oxygen and 5 per cent carbon dioxide, and incubated, with shaking, at 37°C. for 2 hours. In this way we have therefore followed out the general procedure of Shipley and Humel. We found, as they had, that the addition of insulin to the incubated liver slices caused an increased breakdown of glycogen and an increased accumulation of free sugar, over that found in the incubated slice, without added insulin. We have one additional observation to make, which we think may have considerable importance if our speculations can be substantiated in further experiments. In the vessels containing insulin 22 the glycogen concentration of the liver slice fell to about the same value as did the glycogen concentration of the slice in vessels receiving insulin 27, but the amount of free sugar which accumulated in the former vessels was appreciably more than in the latter vessels. And the amount of free sugar which formed in these vessels was considerably above that produced by the observed glycogenolysis. So far we have done no oxygen determinations, and it may be that insulin 22 inhibited the oxidation of free sugar. If we assume that this is not so, then we should like to put forward the tentative suggestion, that this hyperglycaemic factor present in both samples of insulin, but in greater amount in insulin 22, causes not only glycogenolysis but also

TABLE II. GLUCOSE CHANGES IN RAT LIVER SLICES IN VITRO.
EFFECT OF INSULIN

Rat No.	Serum glucose initial mgm. %	Serum glucose after incubation per 100 mgm. of liver slice			Increase in glucose pro- duced per 100 mgm. of liver slice	
		Control mgm. %	Insulin 27 mgm. %	Insulin 22 mgm. %	Insulin 27 mgm. %	Insulin 22 mgm. %
1. —	121	422	515	674	93	152
2. —	159	419	431	826	15	407
3. —	153	320	395	603	75	282
4. —	250	356	347	687	-9	331
5. —	173	348	368	411	20	96

Rat No.	"Total glucose content" of liver slices, gm. %				Glucose produced by glucogenolysis per 100 mgm. liver slice	
	Initial	Control	Insulin 27	Insulin 22	Insulin 27 mgm. %	Insulin 22 mgm. %
1. —	7.21	2.93	2.42	2.35	51	58
2. —	7.33	2.10	1.51	1.538	86	86
3. —	5.91	2.10	1.57	1.55	53	55
4. —	12.56	4.38	4.36	4.18	2	20.
5. —	6.14	2.30	1.76	1.10	51	90

[Balasubramanyam and Waters]

new formation of sugar (gluconeogenesis) (Table II). If we are so rash as to presume this to be a physiological mechanism, then the lack of insulin effect on sugar production which Shipley and Humel obtained with liver slices from fasting rats might be attributed to the fact that gluconeogenesis was already proceeding at a rapid rate and the hyperglycaemic factor would not therefore be expected to make any further appreciable increase. Very recently, Sutherland and Cori (1948)^{2c} have investigated the effect of addition of "Novo" insulin and of insulin preparations containing the hyperglycaemic factor, on rat liver slices incubated in various buffered phosphate solutions. They showed that insulin which had been inactivated, for example, with alkali, still exerted its glycogenolytic action but "Novo" insulin, which possessed no glycogenolytic action, when similarly treated with alkali, did not develop glycogenolytic properties. One wonders whether this might not be regarded as circumstantial evidence that the hyperglycaemic factor may exist as such in the pancreas. In the experiments of Suther-

land and Cori, of the glycogen that disappeared some 60 per cent might be accounted for in terms of the increase in free reducing sugar. There is no evidence in these experiments of any gluconeogenesis. But these workers did not incubate their slices in serum, with its supply of protein and other metabolites, but in inorganic phosphate solutions.

This seems likely to be a fruitful field of experimentation.

There is a further point. You will have observed that we have been using insulin preparations of differing potency. The one at 22 units per mgm. is identical in potency with the international standard of insulin; the other is appreciably higher, namely 27 units per mgm. Whether this difference is wholly due to greater admixture of the less potent preparation with the hyperglycaemic material is not clear. But since the more potent preparation also contains some small amount of the hyperglycaemic factor, we may reasonably predict that insulin preparations assaying at a slightly higher figure than 27 units per mgm. may be obtained. I understand that "Novo" insulin assays at about 23 units per mgm.

In conclusion: it can be stated that methods for the estimation of sugar in blood have steadily improved. Greater reliability has been obtained without unduly increasing the complexity and tedium of the analysis. It is true that we have not got a chemical method specific for glucose: from the very nature of glucose that is understandable, for all methods rely upon its reducing properties. But with the use of various micro-organisms, such as yeast, *proteus vulgaris* and several others a high degree of specificity can be imposed on the relatively non-specific reduction procedures.

We realise that when we determine the concentration of the blood sugar we are really dealing with the equilibrium. Sugar is entering the blood at certain points and leaving it at others. Hormones we know influence these rates of production and removal; and not only hormones for we have seen that even the injection of another sugar, namely fructose, will bring about a profound effect on the equilibrium. Of the hormones we have made some reference to the part played by insulin. We have also dealt with, shall we say, a hormone presumptive or a hormone pretender—the hyperglycaemic factor. It is apparent that there are a multiplicity of factors governing the height of the blood sugar level—and yet how very useful it is to have accurate methods for its measurement.

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Discussions by

FREDERICK M. ALLEN, EDWARD S. DILLON,
THOMAS H. MCGAVACK, and CHARLES H. BEST

continued on next page

DISCUSSIONS

FREDERICK M. ALLEN

Professor of Diseases of Metabolism, New York Polyclinic School and Hospital

In trying to discuss Dr. Waters' very scholarly paper I first take the opportunity to inquire whether he or his colleagues can throw any light on a problem which was discussed in my book published in 1913, namely diabetic polyuria. Although it may vary in early mild cases and in some late cases after the kidney has developed a high threshold or perhaps organic impairment, this symptom is a typical feature of full-fledged diabetes. In contrast to the superficial assumption that glucose is a diuretic, I was struck by the fact that it is not a diuretic when given by mouth, subcutaneously or intraperitoneally. By these routes it is anti-diuretic; it diminishes urine; and only when given intravenously is it a diuretic. This rule holds also for animals which are depancreatized to a degree which does not cause diabetes but reduces the tolerance so that marked hyperglycemia can be produced more easily than in the normal.

Speculatively, I suggested that the glucose given by vein is a crystalloid, but when given otherwise it enters into some kind of linkage so that it behaves as a colloid. But chemists have failed to find even the loosest linkage or to sustain the alpha-beta-gamma distinction or any other difference between diabetic and non-diabetic blood sugar. On the other hand I overlooked the fact that glucose given by vein induces a marked hydremia, altogether different from the condition in diabetes. The failure of a speculative explanation should not distract attention from the observed fact. It may be argued that glucose in the intestine or in the tissues holds water by osmosis, or that glycogen is stored together with water in the normal organism while the diabetic fails to deposit glycogen. But the essential fact is that if adequate water is supplied, the administration of glucose orally, subcutaneously or intraperitoneally causes hyperglycemia and glycosuria accom-

panied by slight hydremia and marked oliguria. This is in contrast to the polyuria which should result from this degree of hydremia without the glucose, and it is opposite to the diabetic condition, in which hyperglycemia is not accompanied by hydremia and the glucose diuresis is so powerful that it can cause polyuria with desiccation of the tissues and concentration of the blood. The seemingly intermediate results in phlorizin or clinical renal glycosuria may deserve study. My impression also is that normal animals injected with sugars which are assimilated poorly or not at all, such as lactose, sucrose, galactose or pentoses fail to equal the diuresis of diabetes. Perhaps these phenomena would be explainable if I had been in position to utilize the recent methods of studying kidney function, but at least superficially the diabetic organism seems to differ from the normal in its handling of glucose not only in the general tissues but also in the kidneys.

On the practical side, I was the first to advocate treating diabetes according to the standard of normal blood sugar, and also the first to contradict the tradition of spontaneous progressiveness of the disease. The two ideas are connected. Also the prevention of progressiveness includes complications. After these many years, there is still need to defend the thesis that diabetes and all its accompaniments can be and should be controlled.

Theoretically, excessive blood sugar is an abnormality, and we should not risk people's lives on an unproved assumption that a chemical abnormality can continue for years without harm. Also diabetes is known to be not merely an over-production of sugar but a defective assimilation; therefore it appears irrational to claim benefit from a high sugar due to lack of assimilation when we have means of improving the assimilation so as to keep the sugar normal.

Hypothetically, the harm of prolonged hyperglycemia might be physical, chemical or metabolic. My previously mentioned book included experiments with long continued injections of cane sugar in cats. The damage to the nervous system, particularly in one animal which became obese, parietic and demented, could perhaps be attributed to the osmotic action of the sugar, and there might be interest in more prolonged and less intensive experiments with a non-assimilable sugar such as lactose with respect to possible arterial lesions. I tried unsuccessfully to break down the tolerance of non-diabetic animals with glucose, but with this method of simple glucose injections Lukens succeeded in producing hydropic degeneration of islands and permanent diabetes in cats. The traditional progressiveness of poorly controlled diabetes is thus clearly explained, and if the pancreatic islands are so sensitive to this clinical stimulus there is reason to suspect some effects on other organs. My own concept is that the metabolic disturbance extends deeper than the mere sugar molecule, probably altering the entire mixture of intermediary products and enzymes. Diabetes is a specific malnutrition. An elevated blood sugar level is chiefly important as the most delicate indicator of this malnutrition. If the malnutrition is long continued, functional and anatomic deterioration may naturally be expected in the blood vessels, nerves and other organs, without the need of incriminating fat or any other single substance as a primary cause. The distinction from undernutrition is illustrated by the pre-insulin experience of clearing up diabetic complications and improving strength by undernutrition or starvation. When either undernutrition or insulin corrects the specific malnutrition according to the most delicate tests, my personal testimony is that the progressiveness and the complications of diabetes remain absent, the degrees of damage which may be present on beginning treatment are arrested, and health is maintained indefinitely.

For testimony other than my own observations, I have had a few illustrative cases examined carefully as to the state of their heart, retina and leg arteries by specialists

in those respective fields. The first of these patients is a 76-year-old man who has had diabetes more than 20 years and whom I have treated for 19 years. He has no subjective complaints, carries on his business as actively as ever, and runs two miles before breakfast every day when the weather is clear. The pulses in his legs and feet are normal. I am showing you an X-ray picture of his legs with no calcification of the arteries. His retina and his heart are reported thoroughly normal. Obviously this man merely happens to belong to a small class of persons who are remarkably well preserved at an advanced age, but the essential point is that his diabetes did not keep him from being well preserved.

I shall omit several similar examinations of patients above the age of 60 who are symptom-free and who show no organic or vascular changes beyond those normal for their years. They merely conform to the rule that persons who are normally controlled remain normal. Some other patients wander away for several years, taking plentiful insulin to maintain weight and comfort but eating carelessly so that sugar is high in blood and urine. They often return on account of retinitis, heart symptoms, gangrene, neuritic pains or other complications. Though some of these conditions are hopeless, control of the diabetes does frequently clear them up and it is always the most important feature of the treatment. Since I find the prevention of these troubles in normally controlled patients to be uniform, without any exceptions, I have been watching for accidental lesions. For example, a certain proportion of elderly persons should be subject to purely arteriosclerotic gangrene, without any diabetic factor. It can only be said that during the past 28 years even the slightest beginning of hypertension has been my indication for reducing or excluding salt in the diet. Also the valuable clinical-pathological study of Wilens, showing an inverse ratio between body weight and arteriosclerosis, implies that the sclerosis is at least to some extent controllable by diet; and the limitation of fat, total calories and body weight was my original principle of diabetic diet. Therefore it is conceivable that, instead of the

traditional excess of arteriosclerosis, there may be a reduction of incidence below that of the general population. At any rate I still can repeat my standing invitation to ophthalmologists and other consultants who see my patients, to point out any one of them who has followed treatment and who develops any diabetic complications.

The next slide shows the photograph of a 14-year-old girl who has had diabetes only 9 years. She is even better looking than her picture. Her eyes, heart and leg arteries are normal. None of her playmates has any happier life or can surpass her in any sport. She illustrates the smooth control of diabetes in a young child with 58 units of insulin daily. I show her partly to place on record a declaration that she will be normal 10 years and 20 and more years from now, and if she marries she can have normal pregnancies.

The final two slides show diabetic mothers and their young children. The first of these is a South American, whose diabetes began 19 years ago, at the age of 16, and I have treated her for 18 years, by occasional check-up visits to this country. Her first pregnancy under the care of local doctors ended in acidosis and abortion. She remained in New York during nearly the whole of her second pregnancy and it was entirely normal. She expects to come here for the same purpose again and I predict a similar result. The second patient became diabetic 22 years ago, at the age of 12 years, and I treated her for 21 years. After having a large ureteral stone removed through a

lumbar incision, she went through a pregnancy which was normal except for large size of the baby. This tendency among diabetics is perhaps explainable as a nutritive effect of the insulin. Because of the handicap of distance for the first patient and the rather difficult fluctuating type of diabetes in the second, their records are not perfect and therefore perfect results are not theoretically to be expected. Prompt correction of irregularities, however, goes far toward preventing complications, both puerperal and non-puerperal. There is no question of the necessity of special treatments after pathological changes have occurred in the arteries and organs. But my impression is that when such changes are found in allegedly well managed cases, examination of the actual records will show hyperglycemia not slight or brief in character but of marked degree for long periods or habitually. My experience is that thorough control of the diabetes from an early stage prevents the specific lesions and eliminates the need for special treatments.

My radical position on the prevention of progressiveness and sequels in both diabetes and hypertension is referred chiefly to the judgment of posterity. This formerly solitary claim seems to be gaining more support from later writers, in proportion as they conform to the methods. But the enormous toll of disability and mortality justifies regret for the long wasted years without the experimental and clinical settlement of this problem which I had once planned.

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EDWARD S. DILLON

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Doctors Waters' paper shows us a sample of the tremendous amount of work which is going on in the field of carbohydrate metabolism resulting in knowledge which has been accumulating rapidly during the past 25 years. As is true in the case of all great discoveries, insulin has posed a great many more questions than it has answered.

I suppose that this audience is composed almost entirely of clinicians, like myself, and I suppose, too, that most of us have trouble in keeping up with all the work and discoveries of our good friends, the biochemists and physiologists. I remember from my own days in medical school, about 35 years ago, that my knowledge of glucose

metabolism was pretty much limited to the fact that one molecule of glucose was oxidized by six molecules of oxygen to produce six molecules of carbon dioxide and six of water. We spoke of the energy supplied to the body by the "carbohydrate fire," as though the oxidation of glucose to carbon dioxide and water was consummated in a single step. Little conception did we have then of the intermediary steps of glucose metabolism: of the anaerobic phase consisting of ten steps from glucose to pyruvic acid in which phosphorylation plays the leading role; of the aerobic phase below pyruvic acid, in which one molecule of pyruvic acid joins with one molecule of oxalacetic acid and goes in eight steps around the Krebs Cycle, the pyruvic acid molecule being entirely broken down and the oxalacetic acid molecule returning to its starting point, ready to take on another molecule of pyruvic acid. All this is a marvelous sequence of chemical reactions, most of them reversible, in which the body receives energy at the relatively low temperature of the body and in the quantities needed at the moment. How different all this is from a "carbohydrate fire"!

Practicing physicians come in touch with blood sugar estimations chiefly under two circumstances, first in the diagnosis of diabetes or hypoglycemia, and second, in guiding the treatment of patients with diabetes.

Frequently, sugar is found in the urine of a patient who has no symptoms and we are called upon to decide whether he has diabetes. The normal figures of the blood sugar tolerance test were established at a time when the blood sugar methods measured copper reducing substances other than glucose as well as glucose. As Doctor Waters has shown tonight, non-glucose reducing substances may be present in sufficient quantities to result in an apparently abnormal blood sugar tolerance test if the method employed measures other copper reducing substances as well as glucose.

The older blood sugar tolerance standards were done on venous blood. Now capillary blood is frequently used. The sugar content of capillary blood is often considerably higher than that of venous blood.

Perhaps we need a new evaluation of

what are to be considered normal figures, using capillary blood and methods giving true glucose values. Fortunately, when the figures are borderline abnormal, the changes which occur with the lapse of time are more important than our opinions as to exactly what constitute normal figures.

The second use for blood sugars which we clinicians have is in connection with keeping our diabetic patients under good control. A single blood sugar determination, if very high or very low, will at once, point the direction our treatment should take. A single moderately elevated blood sugar, 200 for example, may be quite meaningless unless we take into consideration the chief factors which determine the 24 hour blood sugar pattern of this particular patient.

1. Time—When was this blood taken with reference to meals? When was it taken with reference to insulin injections?
2. Insulin—What kind of insulin and how much?
3. Kind of Patient—Is he one whose blood sugar level changes rapidly under the influence of insulin (insulin sensitive) or does his blood sugar level change slowly (insulin resistant)?

These factors must be given careful attention when one is evaluating the meaning of blood sugar reports, or else serious errors are likely to occur. The following are several examples:

- (A) A patient is taking 50 units of protamine daily. Fasting blood sugar is 200. This is not satisfactory because in patients taking protamine insulin the blood sugar level is near its low point before breakfast. This patient needs more insulin.
- (B) A patient is taking 50 units of protamine daily. Blood sugar taken 2 hours after breakfast is 200. This is probably satisfactory as the fasting blood sugar level was probably much lower before breakfast. Protamine insulin usually does not prevent sharp post-prandial peaks in the blood sugar level.
- (C) A patient is taking 30 units of regular insulin before breakfast and 20 units of regular insulin before supper. Fasting sugar is 200. This

is probably satisfactory as this is likely to be the high point of the blood sugar level for the day. Regular insulin is likely to be used up shortly after midnight and the patients own endogenous insulin may be insufficient to keep the blood sugar level down during the rest of the night. The blood sugar may go up during the small hours of the night, even though no food is taken.

(D) A patient is taking 30 and 20 units

of regular insulin as in (C). Blood sugar is 200, taken 2 hours after breakfast. This is not satisfactory as regular insulin is quick acting and should have kept the postprandial blood at a lower level than 200.

Many more examples might be cited. A single blood sugar is always difficult to evaluate and repeated estimations must be made until the 24 hour pattern of that particular patient is established.

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THOMAS H. MCGAVACK

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Dr. Waters has emphasized differences in behavior of simple sugars in blood. While much of what he has said falls far outside the daily routine of the clinician, many pertinent deductions of practical value can be drawn therefrom. For instance, the major portion of galactose must pass through the liver before it is made available in any quantity to function as blood sugar. This remains the fundamental fact of practical importance to the clinician in using some form of the galactose tolerance test for the diagnosis of disease. We prefer to use the intravenous test, which seems to give more reliable and more uniformly comparable results.

This galactose tolerance test proves of most value, as Dr. Waters has already emphasized, in diseases which may interfere with levels of blood glucose and liver function simultaneously. I refer especially to thyrotoxicosis and diabetes mellitus, particularly the form of diabetes mellitus that may be associated with a fatty liver or with diffuse pancreatic disease such as hemochromatosis. The intravenous administration of galactose in such instances and its subsequent periodic determination in the blood affords an accurate gauge of the glycogenic and possibly also of the glycogenolytic function of the liver.

In connection with Dr. Waters' comment on the behavior of the various simple sugars,

one question seems apropos in conjunction with his remarks, and I quote: "While fructose will prevent the decrease in the blood glucose concentration of the liverless animal, there is no increase in the glucose concentration even when large doses of fructose are injected." Does Dr. Waters mean that under such circumstances the muscles and other tissues utilize fructose directly for energy and possible glycogen formation?

Concerning the methods for determining blood sugar, Dr. Waters has stressed those procedures which depend upon copper salts as the oxidizing agents. Does he by implication or otherwise feel that these are in general more accurate than those methods that depend upon the ferricyanide reaction? While we use the copper salt methods exclusively in our laboratories, there are certain modifications of the ferricyanide method such as the "timing method of Van Slyke and Hawkins" that are attractive because of the speed with which they can be performed.

I believe it is usually conceded that glutathione and ergothionine make up the greatest portion of the non-glucose reducing agents while creatinine, uric acid and some undetermined materials the remainder. Inasmuch as Benedict's copper sulfate reagent is probably not reduced by glutathione, this reagent should give rather more accurate results than other reagents. This I believe

is a fairly well settled matter but still one occasionally sees the statement questioned in the literature.

It is certainly important to touch upon the difference between the true blood sugar and all the reducing substances, especially in view of the fact that Mosenthal's extensive studies have demonstrated non-glucose reducing substances in quantities all the way from 1 mg. to 78 mg., with nearly 40 per cent of his subjects showing values above the ordinarily accepted maximum figure of 30 mg. per 100 cc. of blood. Inasmuch as the amount of non-glucose reducing substance may vary from time to time, even within a short space of time, we believe several specimens should be examined in doubtful cases, and the results of fermentation procedures compared with those in which copper salts are reduced. I hope that Dr. Mosenthal will amplify these points himself, so I shall not dwell further upon them.

It seems to us that in any discussion of methods for blood sugar, the problem actually begins, not in the laboratory, but at the bedside. The first point in this regard concerns a dictum rarely stressed, and, I must admit, often violated in our own work. It has been shown that the insertion of a needle into a vein may in a reasonable time, five minutes or so, produce a variation in the value for blood sugar. This affords plenty of time for withdrawing satisfactory specimens. However, usually a tourniquet is used. Within 15 to 30 seconds, this may cause fluctuations, commonly up, but sometimes down, in the value for blood sugar from 15 to 25 mg. per 100 cc. of blood. It seems an important rule, therefore, never to apply the tourniquet until completely in readiness. If venipuncture is unsuccessful at the end of a maximum of 15 seconds, it then should be removed and the procedure tried on the opposite arm.

The next point in obtaining the sample to be tested concerns the timing of our specimen. I shall refer particularly to the diabetic in whom frequent determinations may be desirable. Our aim is to obtain as much information as possible about the condition of the subject with least disturbance to him. Diagnostic punctures are

probably best made in the post-absorptive state, fasting. Further punctures are not necessary in our opinion until the patient becomes aglycosuric. As soon as this occurs both fasting and two and one-half hour post-prandial determinations are desirable to determine both the resting state and the response to the ingestion of blood sugar precursors. Thereafter the post-prandial value gives us an idea of the renal threshold for glucose and serves as a guide to further therapy. As a general rule the older diabetic may show a glucose value at this time up to 250 mg., and sometimes much higher without a spill of sugar in the urine. Further more, the post-prandial figures become both more desirable and valuable, because they can be obtained without disturbing the patient's therapeutic regimen in any way. Perhaps it is trite and forthright insulting to emphasize this really obvious point among physiologists and clinicians, but it is amazing how slow we have been—and I am certainly among the guilty ones—to urge the adoption of this change in routine upon both clinics and hospitals. It may be equally out of place to emphasize the fact that comparative glucose tolerance tests have no part in the management of the known diabetic. However, all too frequently we see such tests ordered. Moreover, comparative tests are of little value unless the patient is on a diet of fixed proportions and amounts of carbohydrate, protein and fat.

Dr. Waters has referred to the effect of fructose absorption upon the concentration of glucose in the blood. In the type of experiment described, does fructose go directly to a levulose furane form or via glucose? I assume the former. Since insulin is necessary for this effect of intravenously administered fructose in lowering the glucose of the blood, a possible explanation may be in the behavior of the fructose and glycogen. The former via a furane levulose form may enter directly into the three carbon stage as described by Cori, Stettin and others, thus never becoming available as glucose. Simultaneously, glycogenolysis may be depressed thus eliminating another source of glucose.

Dr. Waters has touched upon the ability

of the kidney to form glucose, a feat which it seems to accomplish not only from carbohydrate intermediaries but also from amino acids. While, in relation to the total glucose of blood and tissue this function may be small, in some experiments kidney slices in serum have elaborated more glucose than simultaneously prepared and treated liver slices. In any event, the question of the role of the kidney in the regulation of blood sugar deserves consideration. For instance, is it possible that the kidney has played a role in making a portion of the ingested galactose available to the peripheral tissues in the hepatectomized animals mentioned by Dr. Waters? In regard to this effect upon glucose formation, is the kidney subject to internal regulation of an endocrine nature not unlike that of the adrenal cortex? Selye's

experimental work may suggest this. He has shown that, at least histologically, the kidney can be transformed experimentally into a structure of wholly endocrine type resembling the adrenal in appearance and lacking all excretory function.

Finally, there is another point at which Dr. Waters' comments may touch upon the endocrine system. He has mentioned the hyperglycemic factor found even in highly purified preparations of insulin. Does he think this factor plays any part in the production of the clinical state of "insulin resistance"? In view of the short duration of its action, we lean somewhat away from such an hypothesis. However, as insulin formation may be a continuous process, it seems a difficult one to abandon entirely.

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CHARLES H. BEST

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I have been greatly impressed this evening by the familiarity which our clinical friends have demonstrated in the fields of physiology and biochemistry.

I am afraid that Dr. McGavack has posed so many questions to Dr. Waters that another full lecture may be required to answer them.

The President of the American Diabetes Association has shown himself familiar with all the steps in the oxidation of sugar and the formation of glycogen. I suspect that he has learned these rather recently, and many of us are in the same situation.

In connection with Dr. Allen's remarks, I may say, as I have said before, that his book on diabetes was something of a Bible to us in the early days of insulin, and I pay tribute to him as a great clinician, as well as a very productive physiologist and biochemist. It is a great pleasure to see those healthy looking patients of his.

I was at a medical meeting in Toronto not long ago. A young lady, daughter of a close friend of mine, gave a paper. It

so happened that some years ago I lent her father a hand in teaching her to ride and also attended many piano recitals at which she was one of the performers. When I was suddenly asked to discuss her paper at the scientific meeting, I confess I could barely remember what it was about as I was so relieved she had not fallen off or played a wrong note.

Of course, I had no apprehension about Dr. Waters, a senior member of my staff who has always handled himself well, but I do confess that I was somewhat relieved when he stopped telling Welsh jokes and really got down to the subject of the paper of the evening.

I have just returned from the Federation meetings in Atlantic City and I can tell you that I listened to all the papers in two sections. I was chairman of both these sections. I could not get out.

One of the communications was on blood sugar and the young lady who gave the paper was challenged by a member of the audience, who turned out to be Dr. Somogyi.

He asked her about the value which she got. Her reply was really quite adequate. She said, "Sir, I used your recent method and followed it most carefully." There was no further comment.

One of the papers was by Dr. Reinecke, who spoke on the formation of sugar by the kidney. When this process is studied in the intact or hepatectomized animal, there is a definite quantity of sugar formed by the kidney which is however small when compared to that produced by the liver. There seems to be no doubt about the fact that the kidney is capable of gluconeogenesis. The stage has not been reached yet when the influence of the various hormones on this action of the kidney can be studied with much hope of success.

Since the war many of us have been taking stock of the situation in the treatment of diabetes and there are some points on the credit side and some that are not so satisfactory. The mortality statistics have on the whole been better than one would have predicted. On the other hand, many cases in which complications have occurred have been recorded. We are all grateful that more accurate knowledge of the situation has been secured. We realize, however, that much better clinical methods of treatment can be more generally applied. The experimentalist has fallen short of his goal in that he has not made available the best form of insulin, i.e. one which will be liberated in response to need. It is a terribly perplexing situation when a clinician states that he sees just as many complications with the accurate control of blood sugar as he does when the blood sugar in this patient is not accurately regulated. I must say that in many cases the comparison is between poor treatment and moderately good treatment and that the real physiological control of blood sugar is extremely difficult and perhaps at present unattainable in some young children.

On the other hand, Dr. Allen and others

tell us that it is possible in many, perhaps in all of their cases, to secure accurate control and we must watch these patients very carefully. They may lead the way to better treatment of diabetes. Those of us who have worked on the experimental aspects of diabetes feel a great continuing responsibility to attempt to put into the hands of the clinicians the very best tools which can be made available.

We did of course follow a few adult diabetic dogs through five or six years of their lives after insulin became available, and there were few or no complications. We have not as yet followed the puppies, in which the pancreas has been removed, throughout the whole span of their lives, and I hope that this will now be done in many laboratories. If it can be done successfully in puppies and in other species, one will feel fairly certain that similar results can be secured in human subjects. We will be greatly encouraged.

It is very refreshing that a number of groups of experimentalists are studying atherosclerosis. Those of us who are particularly interested in this subject are very pleased that workers can produce cholesterol atherosclerosis in other species than in the rabbit when the basal metabolism is lowered by thyroidectomy or thiouracil. It is extremely interesting that atherosclerosis occurs so frequently in certain species in which the blood fats are normally at a high level. I think that great progress will come in this sphere.

I may predict also that there will be better forms of insulin; that the diet for diabetics will be improved from the point of view of protection against atherosclerosis, and if research workers are permitted to carry on with their peace-time interests, that there will be a still more rapid increase in the rate at which new and useful knowledge in the whole field of diabetes will accumulate.

LIBRARY NOTES

ADDRESS OF ACCEPTANCE AND APPRECIATION
OF THE GIFT OF
THE EDWIN SMITH PAPYRUS

GEORGE BAEHR

President, The New York Academy of Medicine

The Edwin Smith Papyrus is priceless. To quote the great Egyptologist, James Henry Breasted, it is "the oldest nucleus of really scientific medical knowledge in the world." Although its age is more than 3500 years, it is actually a reprint or transcription of an original medical treatise which, from certain words and idioms, can be dated by Egyptologists as having been written a thousand or more years previously.

Almost at the very dawn of recorded Egyptian civilization, perhaps about the time of the Old Kingdom, 5000 years ago when the Pyramids were being erected, a great physician wrote the text of a medical treatise with attention to clinical observation, diagnosis, prognosis and treatment. The Papyrus which has come to us, deals entirely with surgery in a series of forty-eight illustrative cases and it obviously records only part of the original work of the master. His knowledge of anatomy was founded on human dissection and he already knew that blood flowed from the heart through the blood vessels to all parts of the body.

So great was the professional authority of that ancient physician and teacher, that his works continued to be a scientific guide for medical practice for several millennia in that pre-Hellenic era, as did later the

precepts of Galen for another thousand years in the beginning of the Christian era. As Breasted has speculated, he may well have been the original father of medicine, Imhotep, who was later deified by the ancient Greeks as Asclepius (Aesculapius) and from whose teachings Hippocrates derived much of his knowledge of the arts and philosophy of medicine.

The officers and fellows of The New York Academy of Medicine are overwhelmed by the generosity of our great sister institutions, The Brooklyn Museum and the New-York Historical Society. Words cannot express the full measure of our indebtedness. The Edwin Smith Papyrus will be the jewel of our great medical library and a continuing inspiration to scientists and scholars the world over.

In presenting this historic manuscript to The New York Academy of Medicine, I am sure the donors were moved by the fact that the Academy's library has grown during more than a hundred years to be one of the greatest depositories of medical and related scientific literature in existence. Like the famous library of Alexandria before its destruction by the barbarians, it serves today as the very fountainhead of scientific research and medical education. Its 275,000 bound volumes, innumerable pamphlets and more than 2000 current medical and related scientific journals con-

* Given December 2, 1948 at The New York Academy of Medicine.

tain the past and present medical literature of all the nations of the globe. These vast resources of knowledge and learning are freely available not only to all physicians and students but also to the general public as an integral part of the New York Public Library System. It is one of the Academy's essential contributions to the public welfare.

The Rare Book Room of our library, where the Edwin Smith Papyrus will have its permanent place of honor, contains a remarkable collection of old books and ancient hand-illuminated manuscripts through which the evolution of the medical sciences can be traced back to remote antiquity. But lest there be a misunderstanding, let me state that this rare book collection has not been assembled merely to serve as an antiquarian's paradise. It is in fact the

cornerstone of medical science and medical culture, the source of knowledge from which modern medicine has been derived.

We must confess to a deep sense of satisfaction at the confidence in the Academy which you, Mr. Sidney Davidson and you, Dr. Fenwick Beckman, and the institutions which you head, have demonstrated by entrusting this historic document to our care. We accept it as a public trust with a profound appreciation of the enormous responsibility. Our gratitude shall not be expressed in utterances of the moment but by the earnest manner in which we shall forever treasure this precious possession and shall make it freely available to the students and scholars of this country and of the world.

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("Possession does not imply approval.")

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BULLETIN OF THE NEW YORK
ACADEMY OF MEDICINE

CONTENTS

FEB 5 1949

Thoughts on Medical History and Libraries—
1847 and 1947 65
Sanford V. Larkey

Advances in Our Knowledge Concerning the Etiology
and Treatment of Hematological Disorders . . . 84
Cyrus C. Sturgis

A Critique of the Present Status of the Psychotherapies 100
Robert P. Knight

Safeguards in the Use of New Drugs 115
Austin Smith

Medicine Under Hitler 125
George Rosen

Library Notes:
Recent Accessions to the Library 130

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MAHLON ASHFORD, *Editor*

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BULLETIN OF
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FEBRUARY 1949

THOUGHTS ON MEDICAL HISTORY
AND LIBRARIES—1847 AND 1947*

SANFORD V. LARKEY

Librarian, William H. Welch Medical Library, John Hopkins University
and Lecturer in the History of Medicine, School of Medicine.

THE FOUNDING of The New York Academy of Medicine in 1847 was a great event of a momentous year and now in another momentous year we are meeting to celebrate the 100th anniversary of that founding. Centennial celebrations give us a fine opportunity to look back to the past, to make comparisons and to evaluate our present position and plans for the future in light of this agreeably enforced historical viewpoint. The program of this entire celebration with the Institutes covering so many aspects of medicine, so many interests of the Academy, is admirably designed for this end.

It is a great honor and a pleasure to me to have been asked to take part in this program and I propose to take up some of the problems confronting medical history and medical libraries in the spirit of the program of this celebration.

In 1847 we had just seen the victorious end of another war and the

* Read at the Centennial Celebration of The New York Academy of Medicine, meeting of the Section of Historical and Cultural Medicine and of the Friends of the Rare Book Room, March 12, 1947.

beginning of a new era of great expansion for this country. One of the remarkable developments of this period was the great increase in learned societies. It is significant that in 1847, in addition to the Academy of Medicine, the American Medical Association was founded and plans were being made for the American Association for the Advancement of Science, to hold its first meeting in 1848. Many reasons have been given for this movement to found societies. Material factors were certainly of great importance. Although the frontier was expanding rapidly, communications and transportation were at the same time shortening distances, making it easier to arrange meetings. In addition to this factor, Bates¹ has pointed out another—"Americans were becoming a nation of 'joiners'." Societies were being founded for every conceivable purpose or cause. And we still seem to be doing it.

One does not have to conjecture, though, about the reasons for the founding of the Academy. These were expressed very clearly in the early meetings. The primary reason was the growing concern over the state of medical practice and medical education. The aims of the Academy along these lines and the results of its endeavors will be made clear in the various Institutes of this celebration program. But there was another aim that is closer to this group tonight. As Dr. Samuel S. Purple, one of the founders, said at the semi-centennial meeting in 1897,² "But there was still another [object], which was early entertained by the founders, but which did not take on formal development until 1876, and this was the establishment of a great medical library, free to all, one that would fully meet the present and future wants of the medical profession of this great city." One only has to look at this great library with its wonderful Rare Book Room to see how well this aim of the founders of the Academy has been fulfilled.

In going back to the first days of the Academy I immediately wondered if the impact of the earlier Mexican war led to the same mental outlook that we are experiencing today, whether there was the same introspection, the same mingled hopes and fears for the future. It was therefore with great curiosity that I turned to Dr. John W. Francis' *Anniversary Discourse* of 1847.³ Dr. Francis was, as you know, one of the founders and second President of the Academy. While he took a strong stand against the charlatans and the irregular systems of medicine of his day, his main theme was enthusiasm for the achievements of medical research of the preceding fifty years and unbounded

optimism for the future. As he expressed it, "Onward is the watchword, progress is the spirit of the age." A student of medical history, he uses the method of historical comparison to show the great advances of medicine in his time and to answer those who said that medicine was behind the age. Incidentally it is interesting to note that among the American contributions he does not mention the discovery of anesthesia although already the British *Lancet* had hailed it as one of our great contributions along with the discovery of electricity by Franklin. As an historian he also gives us a very valuable series of biographies of New York physicians from the early Dutch days to his own. Throughout one realizes that Dr. Francis feels that he is living in a great transitional era and that great days are just ahead, days in which the newly founded Academy would play a leading role. But of the Mexican war there is only brief passing mention and no indication of what he thought its results would be.

Now here again in 1947, after another war—a far more terrible and devastating war—we find ourselves thinking of what the future holds. As in 1847 great things are expected of science but we are not quite as confident as were the founders of the Academy. Underneath the optimism there is a feeling of uncertainty not only about the political future but about science itself. Along with the hopes for a better life from scientific advances, particularly in the field of medicine, there is also the fear that science may be our undoing. This fear relates not only to the material dangers of atomic energy but also to something deeper, to an effect on our thought and on education.

Today there is a great emphasis on the utilitarian aspects of science and with this a quite generally accepted view that science has and should replace the humanities in our educational program. This trend to replace the humanities by science is bitterly opposed by many thinkers who see in it the danger of a break in the continuity of our cultural background which they feel would lead to intellectual chaos. They believe that a liberal education based on the humanities is essential for real thinking and that too great a stress on science and particularly on its practical side will result in mediocrity, even in the sciences themselves.

Starting from the two extreme points of view there would seem to be little basis for a common agreement, but I feel that here is an issue that must be faced by us, since any solution will greatly affect the

study and teaching of the history of medicine and the future of medical libraries. I propose, therefore, in my discussion first to examine the historical background of this split into two opposing points of view. Then I would like to discuss the place of the history of medicine against this background, its relation to humanistic studies and also its useful role. I will conclude by extending this theme to a consideration of the place of the medical library in our modern world.

The primary feature of the Renaissance was the revolt against the authority of the ancients as it had been systematized in medieval scholasticism. This revolt was the beginning of modern science and was essential for progress. One must, however, examine the corollary that this revolt implied a denunciation of all ancient learning and that hence the study of it was unprofitable.

There were many great 16th century scientists who did not so denounce all ancient learning. While on one hand we have those like the iconoclast Paracelsus who violently opposed all the past, there were many others who appreciated the value of ancient learning and who, although renouncing the false theories and errors of the past, applied its philosophical and experimental methods to achieve their great discoveries.

It should be pointed out that Aristotle and Galen did not establish their own authority. While there is a certain amount of dogma in their works, the rigid authority was given to their ideas by their followers. As Sir Farquhar Buzzard, the late Regius Professor of Medicine at Oxford, once said to me when we were discussing this problem, "It seems to me that Galen has been blamed for a thousand years of progress that *didn't* take place." The key for the disclosure of Galen's errors and the consequent overthrow of his theories already existed in his own works, in his anatomical and physiological methods.

It should also be pointed out in this connection that the earlier phase of the Renaissance, the so-called Humanistic Renaissance, the rediscovery of the original Greek texts of the classics following the fall of Constantinople, was a vital stimulus to the later scientific developments. It was the interest in these more accurate texts that led to a more critical evaluation. Editions in the original Greek were printed and new translations into Latin made, such as those of Galen by Thomas Linacre. In these, new meanings were found which opened up new vistas for further speculation. And also grave errors were un-

covered, again provoking further research and new discoveries. Thus Vesalius, astounded by the errors he had found in the works of Galen, went on to produce his own great original work. It should be remembered though that his approach, his order of presentation and many of his methods were those of Galen.

William Harvey, whose discovery was up to then the most revolutionary in medicine, is at the same time one of the best examples of those who bridged the past and the new. Never a blind follower of Aristotle he still leaned heavily on him, particularly for his basic philosophy and for his methods. He realized that Aristotle and Galen could not have investigated everything and so he sees no discredit to them in pointing out their errors. But nowhere is there denunciation of them or the idea that there should be a break with the past. His discovery, though, was to have this very effect on his followers.

As we go into the 17th century we find more extreme positions being taken. Other factors, political and religious, are assuming a greater importance in the dispute and affect the rationality of the scientific issue. In order to give the coup de grâce to authority the proponents of the new science attack all ancient learning stressing the mistakes and passing by the fundamental truths still valid. On the other hand the more conservative group made an equally extreme and violent defense of the ancients. In so far as this is a struggle for scientific freedom the modern scientist naturally sympathizes with those in revolt but at the same time the other factors should be remembered. One may question whether the fanatical one-sided attack really serves the best interest of science. Perhaps the more temperate attitude, such as is shown in some of the 16th century English mathematicians is more effective.

I would like to say a few words about two of these men as an illustration of this viewpoint, Robert Recorde and Thomas Digges. For some reason these two seem closer to me than some of the men of the later centuries. Possibly this is because I have made more of a study of them but I think it is rather that their ideas are more like our own.

Robert Recorde, a physician, was primarily a great teacher of mathematics. One of the earliest followers of Copernicus in England and a leader of the anti-Aristotelian movement he nevertheless gave due credit to the achievements of the classical scientists. His remark on Ptolemy very succinctly expresses the whole of his philosophy: "No

man can worthely praise Ptolemye, his travell being so great, his diligence so exacte in observations, and conference with all nations, and all ages, and his reasonable examination of all opinions, with demonstrable confirmation of his owne assertion, yet muste you and all take heed, that both in him and in al mennes workes, you be not abused by their authoritye, but evermore attend to their reasons, and examine them well, ever regarding more what is saide, and how it is proved, then who saith it.”⁴

Thomas Digges was a greater scientist. A confirmed Copernican he naturally was opposed to the Aristotelian and Ptolemaic theory of the universe. In 1576 he translated part of Copernicus into English, and in this work he added a concept that was even more shattering to the world of Aristotle—the idea of the infinity of the universe. Yet he too has words of praise for the modesty of Aristotle, blaming his disciples for having more rigid views than their master. Digges in himself represented the two sides of a scientist, the speculative thinker and the practical man. Besides being a great mathematician and astronomer he was also an engineer and an expert in gunnery. But evidently even in his day it was felt that one man could not be both things. He tells an amusing story about this when he tried to bring about a reform in navigation: “First therefore, by demonstrations mathematical finding the great imperfections in the art of Navigation and gross errors practised by masters and mariners of this our age, I sought by reason to persuade with some of them to alter and reform their charts, instruments, and erroneous rules, showing them infallible demonstrations of their errors, . . . I have been answered that my demonstrations were pretty devices, but if I had been in sea services, I should find all these my inventions mere toys, and their rules only infallible. These constant asseverations from men of that profession, even in their own art, did make me half distrust my demonstrations and to think that Reason had abused me, or that there were some such Mystery in sea service, as no Landman’s reason might attain to.”⁵

But he was not to be put off so easily and decided to meet the ‘practical man’ on his own ground. “To resolve myself of this Paradox, I spent a 15 weeks in continual sea services upon the ocean, where by proof I found, and those masters themselves could not but confess, that Experience did no less plainly discover the errors of their rules than my demonstrations.”

These two men were typical of the Elizabethan Age. Always on the search for new horizons they still showed that universality that could combine the speculative and the practical. They did not throw off the past simply because it was old but could use it and build on it.

Let us now turn again to 1847, to see what was the attitude then and whether we can find some help in solving our questions to-day. The *Anniversary Discourse* of Dr. Francis reveals a man deeply grounded in the learning of the past, one who relates it to the problems and the future of a scientific age. To him experimental science was the great force of the age but while extolling it, as one of the primary aims of the Academy, he emphasized its historical development from the past. Thus he says of 'philosophical medicine' "it is only a restoration of the Hippocratic art, corroborated by the great discoveries of modern experiment."⁶ In another place he says, "This, too, is an age of investigation and the rationale of causes is ever sought . . . Theories born in the twilight of past ages are submitted to a more searching alchemy in the crucible of the present. New truth is evolved; old truth confirmed . . ."⁷

He appreciated the influence of other factors in our civilization. He pointed out the "identity of medical knowledge with the progress of society." In a series of historical parallels he shows that medicine flourished most in times of intellectual advance as in the Greece of Pericles, the Augustan age of Rome, under the enlightened Caliphs of Bagdad and similarly in modern European countries in the greatest periods of "advancement in classical and philosophical learning." But medicine had made its own contribution to these advances not only intellectually but above all in its practical application for human well-being. Of this he says: "There is something inexpressibly great in this mutual relation between the cravings of man in his progressive movement, and the support he derives at every stage from the art of healing."⁸

He was keenly aware of the effect of political systems on scientific thought. He pointed out that the great ideas of the 16th and 17th centuries had not achieved their complete development because of existent political systems. As he expressed it: "Despotism opposed an iron barrier to any true relation between the great heart of the people and liberal culture."⁹ To him the great hope for the future was the United States "the very home of free inquiry." He is proud of its past accomplishments and is eloquent in his prophecy of days to come. As a loyal New Yorker he now turns from the country as a whole to

his own city and state. In this transition he exhibits one of the few light touches of his whole speech. Thus he says: "Without considering the motives of the puritan settlers, a theme well nigh exhausted by New-England eloquence, or the chivalric spirit of the southern cavaliers, so nobly embodied in Sir Walter Raleigh, let us turn to those who came from our own fatherland, the scarcely-appreciated home of Erasmus and Grotius."¹⁰ Then follows the series of biographies previously mentioned.

He illustrates the relation of medicine and literature by telling of the friendships between great physicians of the past and the literary lights of their times. He summarizes as follows: "That the healing art is intimately allied with all sciences and the amenities of letters, its history sufficiently demonstrates; and this, indeed, is no small argument for its intrinsic dignity."¹¹

A vigorous proponent of the utmost freedom in scientific research and enthusiastic about the future results of the experimental method, he yet makes a plea for a balanced point of view, that we might take to heart today. Thus he says: "In entering on this march of improvement, so congenial to a sound medical mind, impressed with its responsibilities, an enlightened inquirer of this character will cherish a becoming deference for the wisdom which his predecessors have supplied him, and look with proper caution whither his steps are tending: innovation has its apprehensions, and the utility of reform ought to be urgent. Lord Bacon says it is well to be aware, that it is the reformation that draweth on the change, and not the desire of change that pretendeth the reformation."¹²

When we come to look today at our basic problem, that of the position of science and its relation to the humanities, we find that the situation is not as simple as in the past. On one hand there is not the broad point of view as seen in Recorde and Digges in the 16th century or in Dr. Francis in 1847. Nor is there as clear-cut a drawing of the issue as we saw in the extreme and often fanatical views of the 17th and 18th centuries. Today we do not know just where we do stand. Science is certainly playing a greater and greater role in our life and thought, but all too often it is the practical side that is emphasized. The more speculative side, the true basis of further advance, does not get as much attention nor is it appreciated that there is a fundamental dependency of all science on a broader background of thought.

As science takes this prominent place in our thought there are many who feel we are losing something, something that may be vital. There are different degrees of reaction to this situation. Some feel that it is a natural step in the progress of the human mind, and that the departure of the humanities is of no account. Others, although lamenting the passing of the classics, feel that it is probably inevitable. At the same time they are looking for something else, something resembling the humanities to take their place. They appreciate the importance of the humanistic point of view and feel that in some way this spirit must be kept alive although they do not seem to be willing to keep the real essence, humanism itself, alive. It has been suggested that the history of science should replace the humanities in our curriculum in order to preserve the spirit of humanism. Since, as you will see presently, I believe that the history of science, and as a part of it, the history of medicine, is an integral part of humanistic thought, I cannot accept this solution. You cannot replace the whole by a part. You cannot cut the roots of a tree and expect it to grow.

On the other side of the argument are those who feel that our whole educational program must be based on humanism, in its broadest sense, if we are to turn out really educated, well-rounded people, people who can think and who will have the intellectual capacity for the difficult problems of the future. This view has been admirably expressed in the recent books and articles by Sir Richard Livingstone. While not depreciating the importance of the practical side of science in our professional education, it is his view that the heritage of Western civilization is the guiding factor in our culture. As he says: "Our civilization, spiritual and intellectual, was born in Greece; Rome applied Greek thought to the life and institutions of a great empire; Christianity added new forces which modified and developed its Graeco-Roman inheritance. . . . However ignorant we may be of them, they will mold us. However we may react from them, we bear their marks."¹³ He feels that the student must understand thoroughly the ideas and methods of thinking of the great thinkers of the past in order to understand his own times. :

It is significant that his own humanism is broad enough to include scientific thought. He says, "in reading history as the record of human progress, education must see all three strands in the rope—spiritual, intellectual, political—study the men in whom they are embodied and do justice to all."¹⁴ Thus in the sixteenth century one should study "Sir

Thomas More and Copernicus as well as Henry VIII and Luther.”

As to the situation in this country he cites Walter Lippman's address to the American Association for the Advancement of Science in 1940. In this Mr. Lippman pointed out that we were in an educational vacuum—that there was no common aim or common culture. He feels that the reason that we are so ready to discard the heritage of the past is that we are not willing to make the effort to grapple with it, that we are afraid to face the discipline required to understand it. One must admit that there is a great deal of truth in what he says.

It is not my place here to speak further of the part that either the humanities or science should have in our whole educational program, but I think we are aware that there are disquieting signs in our educational system. There is certainly a dangerous situation in primary and secondary education. The recent series of articles in the *New York Times*,¹⁵ by Dr. Benjamin Fine, gave a graphic picture of the state to which this basic part of our educational system had fallen. He dealt primarily with the physical factors, the lack of buildings and teaching facilities and the incredibly poor salaries paid to teachers. Important as these are, I feel that there are deeper causes for alarm, that there is something wrong with the whole fiber, that, as Mr. Lippman says, there is no aim. I am afraid that we will see the effects of this on science itself and even on the history of medicine.

I will now take up my second point—the position of the history of medicine against this background and what I think should be its role, from the humanistic point of view and from the practical point of view.

The history of medicine and its broader counterpart, the history of science, have always had to look two ways. The history of science is part of science and part of history. Due to the nature of its subject matter it has developed almost independently of the general study of history. Most of those who have in the past written of the history of science have been scientists and it is only fairly recently that general historians have taken up its study. Because of the way in which the history of science has developed, with the emphasis primarily on the purely scientific role, there has been a great tendency to look at the past in light of the present, that is, to look at science as something apart and to study its progress along the lines of its own growth, against the criterion of current validity.

Most histories of science tell of the *great* discoveries—how some

thinker has reached a conclusion far beyond the views held by his fellows. The principal emphasis is placed on the logic of the discovery, and particularly its relation to the views we hold today. A theory that is now discarded, but which in its time may have been current for centuries and exercised a tremendous influence, never has the attention that is given to a view in line with our own.

While it is important to know the history of the great discoveries, this is hardly history in the real sense of the word. It certainly is not history, as the historian knows it, since it leaves out the background of the man of science. It tells us nothing of the way in which the thought of the day or the impact of current affairs influence the scientist. But the scientist is as much a part of his time as the poet or the statesman, and the things he accomplishes are generally related to the conditions and problems of his own day.

Such an approach is not to be deprecated. It is important in studying the development of any science and it stimulates wider interest in the subject. However, it has tended to put science in a place apart and has thus helped in a way to create our present dilemma.

Dr. Owsei Temkin in his thoughtful and provocative *Essay on the Usefulness of Medical History for Medicine*¹⁶ has discussed in some detail the approaches to the history of medicine, telling of the biographical and bibliographical approach, the pragmatic history, the history of diseases and finally the relation to other realms of thought.

The other approach to the history of science, that of looking at the past in light of its own intellectual and social milieu, is coming more to the fore. In this, scientific thought is studied as part of the development of the history of ideas and in its relationship to the interplay of other forces at any given period. One thus could paraphrase the statement of Sir Richard Livingstone in reverse and say that in the 16th century one must remember Sir Thomas More, Henry VIII and Luther as well as Copernicus and Vesalius.

I believe that this humanistic approach to the history of medicine will be followed more and more in the future and that we will see a closer relation to the historical and social sciences. With the ever-widening horizon of modern medicine I feel that greater coördination between the history of medicine and political, social and economic history is increasingly necessary in order that we may understand all the forces influencing the social aspects of our profession.

The meetings that are to take place here at the Academy in the next few weeks illustrate the importance given to this part of medicine. I feel that the history of medicine has a definite function to fulfill, in giving the necessary background and as a focus for bringing together all the elements necessary for a sound solution of our problems.

The history of medicine if it is to be looked at in this way is obviously not something that can be picked up in passing. It will require real study. For it, there must be the broad background of humanistic study, just as I believe there should be for those who expect to achieve real advance in science. The history of science and the history of medicine cannot be expected to supply the untrained student all of humanism as a predigested pabulum. There can be no history of science, no history of medicine without a knowledge of the humanities. The content of thought of the classical literatures and its continuation and amplification as it passed on down the ages is not something that stands apart and that can be thrown away at will. It is a basic element of our life. The great contributions of logical thinking and of philosophical systems are an inherent part of what we think today, in all realms of our culture, in science as well as in literature, history and philosophy. The admission that something *like* the humanities is needed is really an argument for the humanities.

Dr. Henry Sigerist has well expressed this general viewpoint in his recent book of essays, "*The University at the Crossroads.*" He believes "that tomorrow, more than ever, we shall have to emphasize the study of the classics."¹⁷ In another place he says, "If the purpose of the undergraduate school is to give young people a broad general education and to help them understand the world in which they live and in which they are called upon to play a part, the course must include both the humanities and the sciences."¹⁸

I would like now to say something of the more practical aspects of the history of medicine. For we hope to find in the historian of medicine of the future something of the spirit we saw in Thomas Digges, a man who understands the past in its broadest relations and who is capable of speculative thought but who at the same time is aware of the problems of modern medical research. For the history of medicine should be something living and should be able to contribute to scientific research.

The usefulness of history has recently found strong support from a somewhat unexpected quarter. Last Saturday, in what *The New York*

*Times*¹⁹ called "an unprecedented move," the Navy Department called upon educators and historians to help write the naval history of World War II. Both Admiral Nimitz and Admiral King stressed the practical value of history. Admiral Nimitz said "it would be more helpful to our country if more time were spent in trying to predict the future, adding that he "did not mean the 'crystal-ball' method, but the historical one."

I would like to say that the army too has an extensive historical program under way and in this medicine will play a large part. For the past three years I have been working on the medical history of the war and in addition to our aim of wanting to tell a good story of what happened we have always had in mind the practical aspect of our work. As a matter of fact we feel that these two aims are closely related. The more ably the story is told from the truly historical standpoint, the more valuable it will be as a guide to the future. For this reason we have spent a good deal of time in planning the presentation of the history, developing outlines which would give the continuity of events.

It must be realized that this is a different kind of medical history not only because it is current history and so entails a different kind of documentary study but also because it is a military history as well. The basic principles of historiography, however, still apply. There are many facets to such a history: In the first place there is the need to record the actual clinical practices that were used and to evaluate the results and to tell of what discoveries were made and how they can be further applied. These may not be considered as history at all but rather as scientific monographs. They are, however, included in the scope of the historical project. And it is true that the bringing together of the many isolated facts and the attempt to present them in an orderly way involves the historical method. Because of the importance of these clinical results in their practical application it has been decided to separate these studies from the more historical account and every effort is being made to publish them at an early date.

The other part of the story entails a much more thorough application of historical methods. There are so many factors involved in the operation of a great medical service, caring for millions of sick and wounded in all parts of the world and under all sorts of unusual conditions, that great care must be taken to make sure that we are really telling the whole story. Thus, in the history of the European Theatre

we are trying to tell the story of a medical service that supported the greatest military operation in history. This story must be related to the actual military operations for they were always influencing what was happening or was to happen medically. The medical story has to go along with this military story. First there is the long period of building up for the assault across the channel. During this time preparations and plans were being made for the great network of hospitals that was to dot the English country side. These hospitals had to be staffed, supplied and the staff trained for the tasks ahead. All of these elements have to be brought together in the story, they cannot be told separately. Then came the planning for the assault itself and for the campaigns on the continent. This demands a very carefully integrated account if it is to be understood by the average reader. With the actual assault and the campaigns the task becomes even more confusing. There are so many elements all acting at the same time but the aim has to be to relate them all and to tell a continuous story. Such a story brings out many practical aspects and for this reason alone should be useful. I feel that in addition there may be the possibility of applying some of the lessons learned in evolving the presentation of this story to the study of some of the more intricate problems of medicine in our complex life today. The documentary sources of medical history are increasing. In addition to purely scientific works, sources of social, economic and political origin will more and more be utilized.

Medical history can and should play a positive part in scientific medical research. With so many lines of attack and with so many allied fields of science being involved there is great need for some common point of view, some place where a broader outlook can be gained which can serve as a starting point for new approaches. The history of medicine can give this by bringing to research the logical and philosophical ideas underlying the problems in hand. I would like to give an example or two of what this could mean. The study on viruses presents many difficult logical and philosophical implications. The problem is complicated because it brings up at the same time some of the most puzzling concepts of biology, chemistry and physics, each of which has a history and an ideological content of its own. In discussing the basic question, the living or non-living nature of viruses, one immediately thinks of two similar questions of the past, which strangely enough did not seem to be very much connected when they were being fought over then.

These are the problems of spontaneous generation and the struggle between the vitalists and the mechanists. As we look at it now in light of some of the present views on viruses the mechanists probably *should* have believed in spontaneous generation. But here again we must realize that other factors were at work. I think an important step in trying to solve this aspect of the virus problem would be to go back and re-examine the thought on these two basic problems and then to see how these ideas apply to the question today. I do not say that this will solve the problem but it will at least clear the air.

Another concept that has always interested me is that of teleology, the idea of final cause or of purpose in life processes. So often do we hear young physiologists express themselves teleologically, sometimes deliberately as a way of short-cut but many times I am sure without realizing that there is such a thing as teleology. Here again the historical background would give more understanding and at least a clearer expression of ideas. In these and in many other instances the methods of medical history can be applied. These methods have their greatest role in the education of the medical student but I feel that the medical historian can also do his part in an active way in medical research itself.

Dr. Welch, in his essay, "The Interdependence of Medicine with other Sciences of Nature,"²⁰ has pointed out how much the other sciences owe to research in medicine. From the illustrations he gives one can appreciate how important is some knowledge of the history of medicine to workers in other scientific fields. This indicates another useful role for medical history in the future. But at the same time one realizes from Dr. Welch's paper the equal importance of the history of other sciences for the history of medicine. Such study is important not only for the proper understanding of medical history but also in connection with the application of the history of medicine to scientific research. Each of the sciences is becoming so complex that it is difficult for a worker in one field to grasp all the implications in another. The study of the historical development of ideas in these other fields and the relation of them to the medical problem will help in overcoming the difficulty and will lead to greater unification of the sciences.

Now for my third point I would like to say something of the role of the medical library in our modern world. We have already seen what great importance the founders of the Academy of Medicine gave to the library in their plans of 1847 for the future. We all know what

a vital part the Library here has played in the life of the Academy and of the whole country, and will continue to play. I want to emphasize at this time what a great debt the other libraries of the country owe to Dr. Archibald Malloch. I know you all appreciate him here and can see every day how he applies his many remarkable gifts to the complex problems of a great library, but you are not the only ones who benefit. Fortunately, we all can share in his wide learning and his sound sense of values.

During the past two days at the Institute on methods and problems of scientific libraries, so admirably organized by Dr. Malloch, Miss Doe and the staff of your library, we have had many stimulating discussions on the problems facing libraries. These meetings have indicated how seriously librarians are settling to the work ahead. They realize the difficulties but are resolved to face the challenge. Above all, the meeting emphasized the significance of the Library to medical research. I feel that all medical libraries will take an increasingly more important place in the future.

As before in my talk I wish to repeat the same theme, that of the broad cultural significance of a library and its practical contributions. A library is the great repository of the learning of the past. I hope I have said enough to let you know that I think *this* has value. In the great rare book collections, of which the Rare Book Room here is one of the finest in the country the scholar can have direct access to the great classics of medicine and science. Dr. Malloch told us yesterday of the ways used to make the Rare Book Room a more living thing. By extra-catalogues, that is by listing books by printers, by illustrators, by country and chronologically the great treasures take on new significance. Here in these old books the reader can see the thought of great minds unfolding and if he has the insight to look a little further he can see that this is part of a continuous process and that it is related to other elements of our cultural heritage. He may not have to look beyond the book he is reading to see this. If he has before him the 1543 edition of Vesalius he can see the loving care that Oporinus gave to the printing of this magnificent volume. He can learn a lot about the history of printing, how books were printed in the past, how they were put together and bound and what kind of paper was used. He will note the selection of capital letters to fit the subject matter, often with an almost Rabelaisian slant. And above all he will see the remarkable drawings of

Calcar, so perfectly in the tradition of Renaissance art, and the equally remarkable technique of the wood-cut reproduction of the drawings. He should know that most of these very wood-blocks have survived (or did until this last war) and that The New York Academy of Medicine joined with the University of Munich in printing an edition from them in 1934.

If he studies the incunabula he will see how type-faces developed from the script of various schools of producers of manuscripts. He will see how Aldus and the great French printers improved type-faces and will realize what this has meant to modern printing. In short the book is the epitome of the age itself. But for the full appreciation of these books the reader must have some background. These treasures will be wasted if there is no one who can read them and understand them. So again we see the need for a liberal education.

On the practical side I feel that there is a great field for the future in bibliographical research. With the tremendous growth of medical literature in recent years and the extension of medicine into so many overlapping fields there is an ever-increasing danger that we will become lost in the flood of writings. Billings pointed out this danger many years ago but the problem is infinitely worse now. It has reached a state where almost half of the scientific articles published are not indexed or abstracted at all. There should be a thorough study of our index and abstract journals with the aim of division of fields so that there will be as complete a coverage as possible.

Above all though, bibliographical research should be related more directly to actual medical research. Bibliographers should work intimately with the scientific researcher, having an understanding of the problem under investigation but at the same time having the mastery of the bibliographical tools. I realize this is an ambitious program and that it will require a special type of training but I think it will prove economical in the long run.

In our present large-scale plans for scientific research not enough attention has been given to this aspect of research. The bibliographical needs have not been appreciated and little provision has been made in these programs to meet the increased demands that the programs themselves will bring about.

I firmly believe that when the Army Medical Library becomes the truly National Medical Library and finally is housed in a new building

that it so badly needs and must have, that it will have a greater role in bibliographical research. It is embarking on many new projects and these in turn will affect other libraries.

Another program that should be mentioned is that of UNESCO. Plans are being made on an international scale for greater coöperation between the libraries of the world in order to make the scientific and cultural advances of all countries more available to others.

It can be seen that all these programs for the future will call for a much larger number of trained people. It is my belief that we should have some type of training that will give a basic knowledge of the subject of science and of medicine along with the professional skill in library practices and techniques. Only with such a training will the medical librarian of the future be able to cope to the fullest with the problems of the future. It will be objected that this training will take too long. I think this illustrates one of our present fallacies in saving time at the wrong place. Along with what I have said before I think we have to look at our secondary education and relate its aims more clearly to our final end.

This brings me back again to our main theme. In all phases of education we have seen the need for the humanistic approach and I think this applies equally in general education, in medical education, in the study of the history of medicine and in the training of a well-rounded medical librarian. It is necessary if we want to have people of real education but I feel that it will also result in more effective practical ends.

In my talk I have tried to point out what I thought were some of the problems we face today, particularly as they relate to the history of medicine and to medical libraries. I feel that the library and all that it means will continue to be equally as important as the laboratory in the future of culture and of science. I do not think that librarians can fully subscribe to the advice of Louis Agassiz to "read nature not books." If we did we might soon be out of a job. Let us rather take those grand lines of Milton, from the *Areopagitica*, which Dr. Welch so aptly chose to be writ large on the walls of the building bearing his name:

"For books are not absolutely dead things, but do contain a potency of life in them to be as active as that soul was whose progeny they are; nay, they do preserve as in a vial the purest efficacy and extraction of that living intellect that bred them."

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ADVANCES IN OUR KNOWLEDGE CONCERNING THE ETIOLOGY AND TREATMENT OF HEMATOLOGICAL DISORDERS*

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THE most frequently encountered hematological disorder of clinical significance is anemia. Such a state may be defined as a reduction in the hemoglobin, the red blood cell count, or both, below the accepted normal standards. If 15.6 grams of hemoglobin per 100 cc. of blood is considered to be 100 per cent, the lower limit of normal for adult males is 13.3 grams (85 per cent), and 12 grams (77 per cent) for women. The lowest limit of normal for the red blood cell count in males is 4.7 million per cubic millimeter, and for females it is 4.13 per cubic millimeter. Two other levels of the hemoglobin are important to keep in mind. One is 11 grams (70 per cent) which is approximately the level at which the symptoms of anemia (weakness, ease of fatigue, palpitation, dyspnea, and pallor) commonly become apparent; the other is 10 grams (64 per cent) which is the lower limit of normal for the physiological anemia of pregnancy or that which is normally due to increased blood volume with maximum dilution. A hemoglobin level as low as 64 per cent is considered to be normal in a pregnant woman during the latter half of pregnancy.¹

In about 25,000 routine admissions of patients over 14 years of age to the in-patient and out-patient departments of the University Hospital, an anemia of clinical significance, as defined above, was observed in one of every eight patients (12 per cent).² Of these, the most frequently observed (41 per cent) was a normocytic, normochromic type, usually due to chronic infection, and less commonly to chronic nephritis. Next in frequency (39 per cent) was a microcytic, hypochromic anemia due to iron deficiency which is most frequently associated with chronic hemorrhage. The remaining group (20 per cent)

* From the Thomas Henry Simpson Memorial Institute for Medical Research, University of Michigan, Ann Arbor. Read October 8, 1948, before the 21st Graduate Fortnight of The New York Academy of Medicine.

included, for the most part, patients with myelophthisic anemia in association with the various conditions as leukemia, Hodgkin's disease, and different types of cancer; the macrocytic anemias such as pernicious anemia, refractory anemias, and the hemolytic anemias.

Anemia Due to Chronic Infection: This form of anemia is of the normocytic, normochromic type and is usually mild, with a hemoglobin level most frequently in the vicinity of 9.5 grams (60 per cent) and a red blood cell count of 3.0 million per cubic millimeter. The blood picture appears to be surprisingly normal when studied in a stained blood film. Such an anemia is most commonly associated with a chronic infection which causes an obscure disturbance in the metabolism of hemoglobin, thereby retarding its normal rate of synthesis. The infections most frequently responsible are those involving the urinary tract, the female pelvis, and chronic pulmonary infections such as lung abscess and bronchiectasis, osteomyelitis, rheumatoid arthritis, brucellosis, and some patients with *Streptococcus viridans* infection. Rarely has focal infection been of significance. Occasionally, in a growing child, a chronic active sinus involvement may be of importance, but quiescent foci about the teeth or elsewhere play no role in the production of such an anemia.

Another common cause of such an anemia is chronic renal insufficiency. This is usually due to nephritis, associated with an increased nonprotein nitrogen in the circulating blood, but it may be the result of any other cause of renal insufficiency, such as congenital polycystic kidneys.

Improvement in this variety of anemia will not occur with any form of medication unless the underlying cause, whether it be infection or renal disease, is eliminated. Such therapeutic agents as iron, liver, desiccated stomach, folic acid, or any combinations of these medications are valueless. The proper form of therapy is to employ penicillin, streptomycin, or the sulfonamide drugs, either alone, or in combination with surgical measures to control the infection when present. The only other form of treatment which is indicated, when the anemia is severe and the condition of the patient warrants it, is the use of blood transfusions. When the latter form of therapy is decided upon, it is my custom to give a sufficient number to increase the hemoglobin percentage to normal limits. As a rough measure of the number necessary, one may calculate that 500 cc. of blood will increase the hemoglobin

level about 10 per cent. The anemia of nephritis is benefited only by blood transfusions and in my opinion a sufficient number should be given to bring the blood to normal. Usually the patient derives considerable improvement from such therapy.

Iron Deficiency Anemia: This type of anemia is of greatest importance because it occurs commonly, and also because immediate and gratifying results usually follow the oral administration of iron. The diagnosis of such a condition ordinarily presents no difficulties. If a patient has an anemia with a color index in the vicinity of 0.5, a mean corpuscular hemoglobin concentration of 30 per cent or less, and the erythrocytes have an average volume between 55 and 70 microns, it is almost certain that the anemia is due to a deficiency of iron, and that a satisfactory response will be produced by proper iron therapy. Two other anemias may have a blood picture which is similar. They are Mediterranean anemia and a hereditary, possibly sex-linked microcytic hypochromic anemia as reported by Rundles and Falls.³ Both are completely refractory to iron and are so rare in this country that they need not be discussed fully in this communication.

The causes of an iron deficiency anemia may be summarized as follows: 1) Increase in the iron requirement due to growth in infancy, adolescence, and pregnancy and during lactation; 2) Diminished iron reserves in infancy, due to premature birth or iron deficiency anemia in the mother; 3) A dietary intake deficient in iron, observed especially in infancy when the diet may be composed solely of milk; 4) The adverse effect of a subacidity or achlorhydria which lessens the normal rate of absorption of iron; 5) Infection which tends to prevent the synthesis of iron to form hemoglobin; 6) The loss of iron due to chronic hemorrhage especially from the uterus and the gastro-intestinal tract. One of the most common causes of an iron-deficiency anemia in females is excessive menstrual flow, the extent of which is not recognized by the patient. The patient may state, for example, that the periods are "normal" when as much as three or four times the usual menstrual flow may occur at each period for years.

Treatment of Iron Deficiency Anemia: The success of the treatment depends on the following: 1) An iron deficiency must be present; 2) An adequate dose of iron must be given. This may be in the form of ferrous sulfate 0.3 gram (5 grains) three times a day, before meals, orally, which may be doubled in quantity if satisfactory results are not obtained

within two weeks.

Three other points concerning iron therapy should be emphasized. One is that oral iron medication in rare instances may cause gastrointestinal complaints. If this occurs, the ferrous sulfate may be given in enteric coated tablets, or it may be administered after meals, and if necessary the dose may be reduced to one 0.3 gram (5 grains) tablet daily, and increased to the point of tolerance. If the patient is constipated, then ferric ammonium citrate may be given in capsules of 1.0 gram (15 grains) three times daily. A preparation which is usually tolerated well is ferrous gluconate which may be prescribed in doses of 0.6 to 1.0 gram (10 to 15 grains) three times daily. Finally, if the patient has a severe anemia, and all of these measures fail, and this occurs rarely in my experience, blood transfusions may be given. Not only do they supply red blood cells and hemoglobin, but each 500 cc. of blood provides about 250 milligrams of iron.

It is also my firm belief that the proper doses of iron *alone* will accomplish as good results as combinations with preparations such as Ventriculin, liver, folic acid, copper and other substances. In other words, I do not believe that anything can be added to iron which will enhance the therapeutic effect of this metal. Furthermore, in my opinion, there is no place for the parenteral use of iron. This is because it can usually be given effectively by the oral route and second, because when parenteral iron is given in adequate doses, it may be responsible for serious and sometimes alarming symptoms.

Although iron is always indicated in any patient who might have an iron deficiency anemia, special attention should be given to the administration of this element in patients with peptic ulcer on account of the large amount of alkali administered and the tendency to chronic hemorrhage; in pregnancy and lactation and adolescent girls, due to increased needs on account of growth and, in the latter, the presence of menstrual periods; and in donors who repeatedly give blood, especially females, in the period between puberty and the menopause.

The Anemias of Pregnancy: A true anemia of pregnancy may be defined as one due to the gravid state in which there is a greater reduction in the hemoglobin or the red blood cells or both, than that observed in the physiological anemia of pregnancy. The latter is a normal condition due to dilution resulting from the increased blood volume which reaches a maximum of about 26 per cent in the last trimester of preg-

nancy. This dilution effect alone may cause a decrease in the hemoglobin to 10 grams (64 per cent) per 100 cc. of blood, and a red blood cell count of 3.5 million per cubic millimeter.

Between 25 and 50 per cent of all pregnant women have a true anemia of pregnancy, as defined above. Ninety-five per cent of such anemias are of two main types, microcytic or macrocytic. The former is due to an iron deficiency which either pre-exists in the mother prior to pregnancy and is accentuated by the dilution factor, or it is caused by added iron needs associated with the growth of the fetus, formation of the placenta, loss of blood at delivery, and lactation. In some a combination of these factors is active. Such an anemia which occurs in 15 to 30 per cent of all gravid women, is of the hypochromic microcytic type and responds readily to iron medication. Macrocytic anemia of pregnancy may result, in the opinion of Bethell,⁴ from a deficiency of animal protein in the diet. It is usually mild, with a red blood cell count in the vicinity of 2.5 to 3.0 million per cubic millimeter, and a hemoglobin of 7.8 to 9.4 grams (50 to 60 per cent). When the anemia is more severe, it is designated the "pernicious anemia of pregnancy."

These anemias may be prevented by two simple measures. They are the administration of iron and the addition of animal protein to the diet as soon as the pregnancy is recognized. The latter may be accomplished usually by adding a minimum of one egg, a pint of milk, and a serving of lean meat to the regular food intake. If the macrocytic anemia is severe, it may be treated by the oral use of 10 to 15 milligrams of folic acid daily, or the daily use of 4 cc. of crude liver extract intramuscularly. It is of interest that refined liver extract is usually ineffective in this condition, and in one patient treated by Bethell⁵ with vitamin B₁₂ there was no response.

The Macrocytic Anemias: The macrocytic anemias are important, not because they are as common as other types of anemia, but because specific therapeutic remedies are available and recently new ones have been introduced. These anemias include pernicious anemia, the anemia of sprue, the anemia following total gastrectomy, intestinal anastomoses and intestinal stricture, the macrocytic anemia of infancy and pregnancy, the anemia due to widespread liver disease and to dietary inadequacies, and the anemia associated with fish tape worm infestation.

The treatment of choice undoubtedly is the use of refined liver extract (1 cc. equals 15 units) intramuscularly. In relapse the patient

should be given 1 cc. (15 units) three times weekly for two weeks or until the red blood cell count is 3.0 million per cubic millimeter; then the dosage is reduced to 1 cc. (15 units) two times weekly, and continued until the red blood cell count is normal. Following this, 1 cc. (15 units) intramuscularly should be given every two weeks for an indefinite period as a maintenance dose. This should be doubled if 1) there is a persistence or recurrence of the paresthesia of the extremities or other subjective evidence of neurological involvement, 2) if the glossitis is not controlled, or 3) if the patient develops any type of infection.

It is probable that folic acid in daily doses of 10 to 15 milligrams orally, or intramuscularly if necessary, is a satisfactory treatment of sprue, the macrocytic anemias of pregnancy, nutritional macrocytic anemia, and the anemia due to intestinal disturbances. Folic acid, however, is without beneficial effect on the neurological lesions of pernicious anemia and in some cases it appears to accelerate their development. As this is a possibility, it is not even advisable to use the combination of folic acid and liver extract in the treatment of this disease.

Allergy Due to Liver Extract: A small percentage of patients will develop allergic manifestations during the course of treatment with parenteral liver extract, either while the injections are being given at regular intervals, or after they have been omitted and are then resumed. This is an organ rather than a species sensitivity. It should be treated by substituting oral for the parenteral therapy, or even better, by desensitizing the patient to parenteral liver extract. There is a possibility that antihistaminic drugs such as pyribenzamine may prevent the allergic manifestations and they should be given a trial. If vitamin B₁₂ proves to be effective and is available commercially, it may be possible to substitute it for liver extract therapy and thus avoid the allergic manifestations.

Vitamin B₁₂: A new factor (LLD), discovered by Shorb,⁶ and shown by West⁷ to possess the property of inducing hematopoietic remissions in patients with pernicious anemia, has been isolated by Rickes and his associates⁸ and designated as vitamin B₁₂. The intramuscular administration of as small amounts as 1 gamma (1/65000 of a grain) daily to patients with pernicious anemia will produce a maximum reticulocyte rise and an optimum increase in the hemoglobin and red blood cell count of the peripheral blood. Furthermore, it has been shown that it also influences favorably the neurological manifestations.

of the mucous membranes.¹⁰ Injection of this vitamin in a patient with pernicious anemia who was allergic to liver extract produced no untoward symptoms.⁹ The administration of 1 gamma daily to a patient with severe pernicious anemia of pregnancy was not followed by a favorable response although in the same patient folic acid was effective.⁵ The independent isolation of a similar or identical factor with vitamin B₁₂ has been accomplished by Smith.¹¹

Recently Rickes and his associates¹² have discovered that the activity of the compound cannot be separated from its reddish color which is due to cobalt. Furthermore, they have determined that the degree of activity is directly proportional to the depth of this color. West¹³ has demonstrated that this element in the form of cobaltous ion administered subcutaneously either as the acetate or the chloride is without effect when given to patients with pernicious anemia.

Although definitive proof is lacking, it is thought that this vitamin is identical with the erythrocyte maturing factor, that is, the active principle effective in the treatment of patients with pernicious anemia.

Microbial Animal Protein Factor Concentrate: Recently it has been reported by Stokstad and his co-workers¹⁴ that a microbial animal protein factor concentrate, derived from the growth on artificial media of rod-shaped microorganisms present in hen feces, will produce a potent anti-pernicious anemia material. Concentrates of this material produced microbiologically and found to possess animal protein factor activity in the chick also were effective in inducing a hematological remission in patients with pernicious anemia. It is not possible, according to the authors, to conclude that this substance is identical with the material in liver which produces the same effect in humans. It is their opinion, however, that the bacterial extract may contain complexes of the anti-pernicious anemia factor which are utilized by chicks to produce the animal protein factor, and less effectively by patients with pernicious anemia as sources of anti-pernicious anemia factor.

The Etiology of Pernicious Anemia: Since the discovery of folic acid, and more recently of vitamin B₁₂, the entire subject of the etiology of pernicious anemia has been reopened for consideration. Following the irrefutable observations on the etiology of this condition by Castle in 1928, it has been clearly established that some unidentified material in the diet is acted upon by a component of the gastric juice to produce a substance which controls the maturation of the red blood cells in the

bone marrow.

If vitamin B₁₂ is considered to be the anti-pernicious anemia principle, the difficulty arises chiefly with our incomplete knowledge as to how to incorporate into Castle's theory, the function of folic acid and its conjugates. A purely tentative explanation would be that 1) the extrinsic factor in the food reacts with 2) the intrinsic factor in the gastric juice, to form 3) the active principle which may be vitamin B₁₂. This material which is stored in the liver is concerned, among other functions, with the release of folic acid from its conjugated form. Folic acid is required for the normal production of red blood cells. This theory is subject to revision upon the discovery of new information. It is obviously incomplete as an explanation is not provided to account for the degenerative changes in the nervous system which are probably due to the lack of some necessary substance essential for the maintenance of normal nutrition of the nerve cells.

Agranulocytosis: Agranulocytosis is not a common disease but it should be kept in mind constantly because it is probably always due to a drug sensitivity, and its early recognition and prompt treatment is essential in order to avert fatalities. Although a great majority of cases are due to sensitivity to some drug, occasionally it is not possible to demonstrate the causative factor. The following are known to be responsible for the disorder: 1) the sulfonamide drugs, including sulfanilamide, sulfapyridine, sulfathiazole, sulfadiazine, and succinyl sulfathiazole; 2) thiouracil and rarely propylthiouracil; 3) aminopyrine and closely allied products as novaldin and causalin; 4) gold; and 5) arsenphenamine. It has been claimed that other drugs may cause this condition but there is no substantial proof in support of this. Recently it has been reported that Tridione, an anti-convulsant agent, may cause a severe leukopenia but this is in association with other evidences of aplastic anemia, namely, a reduction in the platelets and red blood cells.¹⁵

A word of advice is pertinent in regard to this disease. When a patient is receiving a drug which is known to cause agranulocytosis, it should be made clear that if a sore throat, skin rash, chills or fever develop, then the drug should be omitted promptly, and a white blood cell count obtained. If this is decreased significantly, then energetic treatment with penicillin, 40,000 to 80,000 units intramuscularly every three hours should be given. Death in this condition is always due to

sepsis but if the disease is detected in its early stages, the causative drug eliminated, and penicillin given, it is unlikely that any patient will succumb to the condition.

Nitrogen Mustard Therapy: The most satisfactory routine treatment of Hodgkin's disease, lymphosarcoma and chronic leukemia, is roentgen irradiation. In Hodgkin's disease especially, when this becomes ineffective, the physician would be denying the patient an opportunity for further improvement if nitrogen mustard therapy¹⁶ were not given. In at least two-thirds of such patients, this chemotherapy will result in distinct but regrettably brief remissions. These are indicated by temporary subsidence of fever, regression of the lymphadenopathy, hepatomegaly, and splenomegaly, and an improvement in the cutaneous manifestations. The remissions persist from a month to eight or ten months, and in occasional instances for longer intervals. It is not possible, however, to predict the duration of the salutary effects in any given patient. Further, there is some evidence which suggests that patients with Hodgkin's disease who have become refractory to roentgen irradiation may be resensitized to it by nitrogen mustard therapy. Also the latter form of treatment is useful in the occasional patient with Hodgkin's disease in whom intensive roentgen ray therapy to the mediastinum is desirable but in whom fibrosis to the lungs develops. In such patients, the nitrogen mustard therapy has no such adverse effects on pulmonary tissue.

The drug produces some beneficial results in patients with chronic myelogenous and lymphatic leukemias, and has been tried but without significant benefit, in the acute leukemias. While it does produce remissions in some patients with chronic leukemia, in polycythemia vera, and in lymphosarcoma, the results attained are not comparable with those produced by irradiation. One of the most recent publications dealing with the therapeutic effect of the nitrogen mustards is that of Zanes and his co-workers.¹⁷

It has been our custom to administer nitrogen mustard in a dosage of 0.1 milligram per kilo of body weight, every other day for four doses, but in no instance to give more than a total dosage of 24 milligrams in any one course. Following each nitrogen mustard injection in the form of the methyl-bis compound, there was rather distressing nausea and vomiting which persisted for six to eight hours. The new preparation, SK 136, the chemical name of which is 1,3,-Bis [Bis-

(Beta-Chloroethyl)] Aminopropane Dihydrochloride, when administered in the same dosage, is equally effective and does not produce these symptoms. Almost immediately following its injection, however, there is anorexia, depression and malaise of appreciable extent which may persist for 12 to 24 hours. Another untoward effect of chemotherapy is thrombosis of veins following the intravenous treatment. This may be averted by injecting the medication directly into the rubber tube through which normal saline is flowing into a vein. Undoubtedly the most serious complication of the treatment is the transitory destructive effect on the hematopoietic tissue. This manifests itself within 4 to 5 days following treatment by a decrease in the red blood cells, the white blood cells and the platelets of the circulating blood, and continues for about 3 to 4 weeks. In one of our patients with Hodgkin's disease, the total white blood cell count fell to 250 per cubic millimeter, but in most instances the decrease is much less than this. This untoward effect on the bone marrow is temporary, and all evidence of it usually disappears within a few weeks. It should be emphasized, however, that the margin between the therapeutic and toxic dose which might be responsible for serious damage is slight, and hence the drug should be used in all cases with caution.

Leukemia: While various new forms of therapy have become available recently, it has not been demonstrated that they prolong life significantly. Their use is amply justified, however, by the relief of symptoms and increased activity of the patient. No one would deny a patient the striking improvement which follows treatment, even though it is transient. Roentgen ray irradiation still remains the most satisfactory treatment for routine use. This is because it is more generally available, its dosage is easily controlled, and after many years of experience, its effects are predictable with greater certainty. In the past this therapeutic agent has undoubtedly been given to patients with leukemia in excessive dosage, with resultant harm to all the hematopoietic elements of the body. While the success of irradiation depends on the greater sensitivity of the leukemic cells to it, as compared to the erythrocytes and platelets, the difference between a toxic and therapeutic dose is slight. Hence the minimal dose which gives the optimum effect should be employed.

In my opinion, patients with chronic myelogenous leukemia should be treated with the "spray" or total body irradiation technique. An

exception to this is in patients whose outstanding complaint is pain in the region of a greatly enlarged spleen. This may be promptly relieved by the localized irradiation over this area. The dose should be small when the "spray" technique is used, not to exceed 150 roentgens during a single course of treatment, over a period of two weeks. Patients with chronic lymphatic leukemia appear to respond more satisfactorily to the localized form of treatment.

In my opinion, one mistake which has been made in the past is in permitting the symptoms of relapse to progress too far before additional therapy is given. With the earliest symptoms of relapse or, in the absence of symptoms, with the elevation of the white blood cell count to 40,000 per cubic millimeter, serious consideration should be given to further roentgen therapy.

Radioactive phosphorus, P^{32} , is another form of systemic irradiation which is of value in the treatment of chronic leukemia. When given in single doses of 4 to 6 millicuries intravenously and repeated, if necessary, in the same dosage in not less than four months, the results are comparable to those produced by the roentgen ray. Such treatment possesses no advantages, however, except that it is easily given, and there is an absence of irradiation sickness. On the other hand, as the situation is at present, it requires certain apparatus and experienced workers to control the administration of the preparation, and caution must be used in its use. Certainly it cannot be said that the practitioner is depriving the patient of a superior form of treatment, if roentgen ray therapy is given instead of radioactive phosphorus.

Urethane in the Treatment of Leukemia: In 1946 Paterson and her associates¹⁸ reported the favorable effect of urethane (ethyl carbamate) in patients with leukemia, and concluded that this drug produced comparable results to those observed following the use of the roentgen ray. Although the exact mode of action of urethane is unknown, it is thought that its favorable effects are produced by inhibition of the rate of mitotic cell division of neoplastic cells. Recently a summary of our knowledge on this subject has been published by Berman and Axelrod.¹⁹

Our results in a series of patients have been promising. Treatment has been as follows: enteric coated tablets, 0.32 gram (5 grains) each, are given three times daily. On successive days the dosage is increased to a total of 4, 5, 6, 7, 8, 9 such tablets daily, with a maximum daily dosage of about 3.0 grams (45 grains). If this dose is tolerated, it

should be continued, preferably until a normal white blood cell count is reached. The dose should be decreased if gastro-intestinal symptoms are provoked.

It requires from 15 to 90 days, with an average of 21 days, for the leukocyte count to fall to normal. The white blood cell count should be determined every two to three weeks, and when it reaches normal the dose should be reduced to 1.0 gram (15 grains) daily.

The present experience with the use of urethane in the treatment of leukemia does not warrant a final conclusion. It is a simple therapeutic measure which has promise of effecting changes similar to those induced by irradiation. The possibility of harm resulting from over-treatment makes it necessary for the patient to be under observation, and the leukocyte count should be determined at intervals. Some believe that urethane is resolved into urea and carbon dioxide in the body. If this is so, consideration should be given to the possibility that injury might result from an accumulation of blood urea in patients with kidney disease when this drug is employed in the doses advised.

In our patients, especially those with chronic myelogenous leukemia, gratifying improvement occurred in a majority of those who received this treatment. Patients with lymphatic leukemia responded less satisfactorily. It is difficult to state the duration of the remissions which are induced, but in one of our patients it has exceeded a year. Although the white blood cell count is frequently reduced in patients with acute leukemia when urethane is given, the general course of the disease does not seem to be influenced.

Folic Acid Antagonists: Recently a number of compounds closely related to folic acid, have been developed which have the property of actually inhibiting the growth-stimulating action of folic acid toward certain bacteria by interference with enzyme systems. The effect of such antagonists, as they are called, in acute leukemia was first reported by Farber and his associates in June of 1948.²⁰ During the past few months Bethell and others²¹ have treated a group of patients with leukemia and related disorders with aminopterin, a folic acid inhibitor (4-aminopteroyl glutamic acid). In patients with myelogenous leukemia, the most important change was a fall in the granulocyte count of the peripheral blood, and a progressive decrease in myeloid activity of the bone marrow as shown by sternal puncture. Prolonged administration of larger doses appeared to depress the formation of the erythrocytes.

In some patients with myelogenous leukemia there was a notable decrease in symptoms, and the size of the spleen. On the discontinuance of the therapy, increased activity of the leukemic process rapidly recurred. In one patient, it was possible to reverse the action of the antagonist by the administration of folic acid in large doses.

Our observations indicate, in general, that in adults with acute leukemia the effect of the antagonist is to convert the condition to an aplastic anemia. There appears to be a "wiping out" of the granulocyte series. The action of the antagonist is not entirely salutary as indicated by the development of ulcerative lesions in the mouth and the appearance of alopecia in some patients. It is possible this may result from the action of the antagonist on other components of the vitamin B complex.

The preliminary studies do not indicate that the course of the disease is materially altered by aminopterin therapy although promising results have been observed in children with acute leukemia. It is possible, however, that a preparation with such a unique and powerful action may be altered to provide a more effective control of the leukemic states.

Polycythemia: This condition may be treated satisfactorily by the use of three therapeutic measures, as follows: 1) Phlebotomy, with the reduction in the hematocrit to 50 per cent or the removal of a total average amount of 1500 cc. of blood at the rate of 300 to 500 cc. every third day; 2) the use of total body roentgen irradiation with treatment every other day until the white blood cell count is below 4,000 per cubic millimeter; and 3) the use of radioactive phosphorus in a dose of 4 to 6 millicuries intravenously, not to be repeated for a period of four months.

It is often advisable, if the patient is suffering from acute symptoms of polycythemia, to remove a sufficient quantity of blood, as indicated above, to make the patient comfortable and then give either roentgen or radioactive phosphorus irradiation. Total body irradiation will control the disease satisfactorily²² although it may be necessary to repeat the treatment in several months. In some patients, however, additional therapy is not necessary for two years. The ideal treatment appears to be with radioactive phosphorus which can be given easily, and often the patient is maintained in good condition without additional therapy for three years or more.

The question has been raised that irradiation, especially with radio-

active phosphorus, may increase the possibility of transforming polycythemia into leukemia. It has been known that such a transformation does occur spontaneously and there is no proof, in my opinion, that the use of radioactive phosphorus makes it more likely.

Hemolytic Anemias: If the diagnosis of hemolytic anemia is established, and such causes as infection, chemicals and others are excluded, then an attempt should be made to differentiate between the two main varieties of the condition, namely the congenital and the acquired. If another case exists in the blood relatives, that is, of course, strong evidence in favor of the hereditary type. In addition, the following diagnostic points are of assistance, but are not absolutely conclusive, in differentiating between the two. In congenital hemolytic anemia, the active manifestations of the disorder are noted in childhood, microspherocytes are usually present in the circulating blood, and there is always evidence of increased fragility of the erythrocytes. On the other hand, in acquired hemolytic anemia, the symptoms are not likely to appear until adolescent or young adult life; spherocytes are not commonly present; increased fragility of the erythrocytes is observed in only 40 per cent of the cases; frequently there is hepatomegaly and often there is enlargement of the lymph glands; a leukopenia is commonly present; and not infrequently there are a few abnormal lymphocytes and monocytes in the circulating blood.

In the congenital variety, the results of splenectomy are uniformly satisfactory provided accessory spleens which may be present, are also removed at operation. Splenectomy is advisable, therefore, as soon as the diagnosis is established. In patients with acquired hemolytic anemia, surgical treatment is not always indicated because the condition may be due to some cause such as drugs or to infection, and also because even in the idiopathic type, the operation is helpful in only about two-thirds of the patients. When a patient with the acquired type is encountered, therefore, great care should be employed to exclude all known causes. If this can be done, then the patient should be observed for a few weeks to determine if his condition is improving, remaining stationary, or progressing. If the latter is the case, then splenectomy is indicated.

It should be kept in mind that severe and even fatal hemolytic reactions may occur in patients with hemolytic anemia following blood transfusions, even though all precautions have been taken in matching

the blood of the donor with that of the recipient. Blood transfusions are indicated, nevertheless, in such patients in some instances before operation, and also in periods of rapid destruction of blood with associated hemolytic shock, and they can often be given safely. The following procedure is advisable. After careful matching, 50 cc. of blood should be given slowly. The transfusion is then discontinued and the patient observed for an hour. If no untoward reaction occurs, then the remainder of the blood may be administered over a period of two to three hours. The importance of this is emphasized by the knowledge that about 50 per cent of patients succumb who have received 500 cc. of incompatible blood. On the other hand, the hemolytic destruction of 50 to 100 cc. is rarely if ever associated with a fatal outcome. If a patient with hemolytic anemia is in shock and cannot be given blood transfusions on account of destruction of the injected red blood cells, then plasma transfusions should be employed liberally to combat the condition.

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A CRITIQUE OF THE PRESENT STATUS OF THE PSYCHOTHERAPIES*

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BEFORE ONE can write a meaningful critical evaluation of the psychotherapies of today, he must attempt to define the types of treatment methods which are commonly assumed to be distinguishable varieties of psychotherapy. This is no easy task, for there exists no such generally accepted classified listing of the psychotherapies. A motley array of adjectives is found to designate brands of psychotherapy which are supposedly different from each other but which actually overlap each other in manifold ways. It will be a necessary preliminary task for us to review the terms commonly used in psychiatric literature and in ordinary professional parlance to designate various types of psychotherapy.

In a survey of usages which probably falls short of being exhaustive, I have noted that the type of psychotherapy may be characterized from any one of a number of frames of reference:

1. With regard to the preponderant attitude taken or influence attempted by the therapist; e.g., suggestion, persuasion, exhortation, intimidation, counselling, interpretation, re-education, re-training, etc.
2. With regard to the general aim of the therapy; e.g., supportive, suppressive, expressive, cathartic, ventilative, etc.
3. With regard to the supposed "depth" of the therapy—superficial psychotherapy and deep psychotherapy.
4. With regard to the duration—brief psychotherapy and prolonged psychotherapy.
5. With regard to its supposed relationship to Freudian psychoanalysis, as, for example, orthodox, standard, classical, or regular psychoanalysis, modified psychoanalysis, wild analysis, direct psychoanalysis, psychoanalytic psychotherapy, psychoanalytically oriented psychotherapy, psychodynamic psychotherapy, psychotherapy using

* Read at the Twenty-First Graduate Fortnight of The New York Academy of Medicine, October 6, 1948.

the dynamic approach, and psychotherapy based on psychoanalytic principles.

6. With regard to the ex-Freudian dissident who started a new school of psychotherapy. Thus we have Adler's individual psychology with its Adlerian "analysis," Jung's analytical psychology with its Jungian "analysis," the Rankian analysis, the Stekelian analysis, and the Horney modifications.

7. With regard to whether patients are treated singly or in groups—individual psychotherapy and group psychotherapy.

8. With regard to whether the psychotherapy is "directive" or "non-directive," an issue emphasized strongly by the Rogers group of psychologists.

9. With regard to the adjunctive technique which is coupled with psychotherapy; e.g., narcotherapy (narcoanalysis, narcosynthesis), and hypnotherapy (hypnoanalysis), the first using drugs and the second hypnosis for technical reasons to be discussed later.

It is not surprising that both physicians and the lay public regard this welter of terminology as something less than scientific, and that patients seeking help for emotional distress are often confused as to where to find that help and as to what type of psychotherapy to trust. In defense of the present confusion one can remind himself that although psychotherapy is said to be the oldest form of medical treatment, it is also one of the very latest to achieve a scientific, rational basis, i.e., to rest on a basic science of dynamic psychology. Because of its partial derivation from many unscientific and extra-scientific sources—primitive magical practices of tribal medicine men, religious rites, parental exhortations and commands, mysticism, common-sense advice and intuitive insights of friends, and downright quackery, to mention but a few—psychotherapy has among its practitioners today not only many lay fakirs but also a good many physicians whose training in dynamic psychology is grossly inadequate. Also, even among the best trained psychiatrists there exist some honest differences of opinion regarding principles and techniques of psychotherapy. However, research and experimentation continue to expand, and slowly the phenomena of artful and intuitive psychotherapeutic influence are translated into scientific principles and techniques.

It is impossible to overstate the importance of dynamic psychology as a basic science on which all competent psychotherapy must rest.

Without an underlying structure of psychodynamics and psychopathology, in which the psychotherapist must be well trained, all psychotherapy is at best empirical, at the worst the blind leading the blind. No valid critique of the psychotherapies is possible except in relation to the penetrating understanding of human personality and behavior provided by dynamic psychology, the chief contributions to which have been made by psychoanalysis.

It seems necessary, therefore, to review for an essentially non-psychiatric medical audience the theoretical essentials in modern dynamic psychology. The cornerstone of dynamic psychology is the concept of repression. As the psychic structure of the human personality develops in infancy and childhood, the primitive erotic and aggressive impulses come to be opposed by counter-impulses deriving from the child's training and adaptive experiences. The chief counter-impulse is repression, which banishes from consciousness—but not from continued active existence in the unconscious—those impulses, some native and some stimulated by specific experiences, which the child discovers are condemned and forbidden expression by its upbringers. Both the strength of the alien impulses and the child's capacity to oppose them are partially determined by his native constitution, partly by the nature of his early experiences, and partly by the character and upbringing methods of those adults who rear him. Some condemned impulses are simply repressed, along with their associated fantasies and affects; others are modified in partial expression and partial repression, assisted by other defense mechanisms. Topographically the unconscious is regarded as the repository of repressed impulses and forgotten memories, the preconscious as that part of the mind in which reside the rememberable but currently unattended to memories, and the conscious mind as the aware, focussing, thinking portion of the psychic structure. Viewed dynamically, the primitive impulses arise out of biological and psychological drives identified collectively as the Id, while the opposing, defensive forces arise from Ego, or organized part of the personality, and the Super-ego—roughly the conscience. The sum total of these dynamic internal and external interactions, plus constitution and native intellectual endowment, equals the developing personality in all of its individual uniqueness. While the major battle between opposing internal forces appears to be settled at about age five or six, thus forming the basic personality structure, there is a continuous internal interaction

and a constant external adaptive attempt throughout life, with special crises during adolescence and in reaction to the Protean forms that stressful life experiences can take. Also, each individual, however healthy his adaptation appears to be, has his own particular psychological areas of vulnerability to stress, and he may be precipitated into clinical neurotic or psychotic illness by experiences whose qualitative or quantitative nature exceed his capacity to master them through healthy adaptive methods.

This highly condensed exposition of dynamic psychology with its emphasis on the uniqueness of the individual will, I hope, be sufficient to serve as a background for the following proposition, namely, that competent treatment of a patient by psychotherapeutic means requires of the psychotherapist:

1. That he be thoroughly grounded in the basic science of dynamic psychology.

2. That he be well trained in clinical methods of evaluating the individual patient, not only in terms of general comparison with others presenting similar clinical pictures, but also in terms of the uniquely individual forces and factors in each individual patient.

3. That he then utilize, from among the available psychotherapeutic approaches and techniques, those particular ones which, according to his best clinical judgment, are most appropriate in a given case.

4. A fourth prerequisite does not follow logically from the previous argument but is of an importance at least equal to the other three, namely, that the psychotherapist be a person of integrity, objectivity, and sincere interest in people, and that he be relatively free from personal conflicts, anxieties, biases, emotional blind spots, rigidities of manner, and settled convictions as to how people should properly behave.

This last prerequisite for psychotherapeutic work requires some amplification. Unlike the situation in other fields of medical therapy, the man well grounded in the basic science underlying his therapy, well trained in diagnostic methods, and possessing technical competence to use the indicated therapy may still, in psychotherapy, be a poor practitioner if he is personally anxious, rigid, or full of moral convictions. Other therapies in medicine can be competently performed, with good results on patients, without these personal qualities, largely because a great deal of medical and surgical treatment consists of doing some-

thing to the patient. To be sure the personal qualities in a physician which cause his patients to love and trust him are exactly the ones which make him a real physician rather than a mechanical artisan; but far greater emotional demands are made on the psychotherapist. The nature of the subject material in psychotherapy, the intense personal give and take in the patient-therapist relationship, the enormously increased possibilities of anti-therapeutic personal involvement, the self knowledge in the therapist required both to understand his patients and to steer a sound therapeutic course with them, all require of the psychotherapist certain personal qualities not essential to other medical specialists. It is not particularly difficult for physicians to acquire protective attitudes of detachment in respect to those bodily elements and products—blood, pus, urine, diseased tissue, mucus, feces, guts—which so upset the squeamish layman, and this detachment serves the physician in good stead as he works coolly and efficiently at his therapeutic task. But this sort of detachment in a psychotherapist is not only no protection against the psychological products of his patients, it actually hampers and distorts his therapeutic work and, if extreme, even disqualifies him from undertaking to deal with psychopathology and psychotherapy. The counterphobic attitude may be sufficient for competent work in physiology, pathology, and surgery; it is a poor and brittle defense for work in psychiatry and psychotherapy.

Such personal considerations with regard to the psychotherapist raise important questions regarding selection of candidates for psychiatric training, and regarding the importance of personal psychoanalysis as a part of psychoanalytic and psychiatric training. Certainly every psychiatrist who wishes to do psychoanalytic therapy should have full psychoanalytic training, including, of course, the personal analysis. It might also be said that every psychiatrist who expects to practice major psychotherapy of any kind should have full psychoanalytic training, just as every physician who plans to do major surgery should have full surgical training.

I have so far attempted to show that the terminology designating supposed varieties of psychotherapy is very confusing because of the many frames of reference in which identifying adjectives were applied, and to indicate that a critique of these psychotherapies is not possible until a valid frame of reference is established. I then tried to show that familiarity with the basic science of dynamic psychology, and the

clinical techniques derived from it is necessary to provide a valid frame of reference for a critique. This led to the collateral but vital point of the psychotherapist's personal suitability. It is necessary to establish one more phase of this frame of reference. This has to do with the nature and vicissitudes of the patient-physician relationship in psychotherapy.

Most physicians are not much concerned about the attitudes, emotions, and fantasies their patients have about them as long as the patients are coöperative, don't go to other physicians, and pay their bills for professional services. Occasionally physicians are startled to encounter outbursts of unprovoked hostility or professions of love or jealousy, or suspicion from their patients. I suppose the usual result is that the patient is then discharged by that physician in the event the physician cannot "talk him out of his nonsense." Many psychiatrists of the past (and some in the present) have been more concerned about emotional reactions of patients to them, but have thought of them in terms of "good rapport" or the lack of it, without paying much attention to the exact nature of these reactions, whether friendly or hostile. Sigmund Freud, picking up a cue noted but abandoned by Josef Breuer, had the genius to follow through to a penetrating study of patients' emotional attitudes toward their doctors and to bring this group of phenomena into both the theoretical framework of dynamic psychology and the clinical framework of psychotherapy. He saw that whereas the various emotional reactions of the individual patient appeared at first to be irrational and unprovoked, actually these attitudes could be understood the same as other psychological phenomena in the patient could be understood, such as recovered memories, dreams, fantasies, and so on, and could, instead of being emotionally reacted to by the therapist, provide him with material for fresh insights into his patient. Freud called these reactions "transference" because of his understanding of them as emotions originally felt toward other significant persons in the patient's past experience, and now transferred to the doctor. He discovered that their nature could be interpreted to the patient, and that such interpretations, when correctly timed and accurately expressed, had significant therapeutic effect on the patient. Thus the theoretical understanding and clinical use of transference phenomena became one of the significant contributions of psychoanalysis to the field of psychiatry, and, indeed, to the practice of medicine in general, for trans-

ference reactions by patients are by no means limited to those being treated psychotherapeutically.

Freud also had the objectivity to observe and analyze his own reactions to patients, and concluded that all psychotherapists would have their own particular tendencies to react inappropriately (that is, inappropriately from the standpoint of correct therapeutic technique) to the material, or behavior, or persons of their patients. He called such reactions and reaction tendencies "counter-transference," and bade all analysts to be acutely observant of themselves in this regard so that they might analyze and dissipate these counter-transference reactions without letting themselves be unwittingly influenced by them to the detriment of their therapeutic efforts. Again, such counter-transference reactions are not confined to psychiatrists, psychoanalysts, or psychotherapists, but are present in all physicians toward their patients, albeit with considerably less significance, for the most part, in therapy other than psychotherapy. Once more, then, we see the importance for the psychotherapist of those personal qualities of integrity, objectivity, sincerity, and relative freedom from emotional blind spots.

I have now used almost half of my time to develop the background frame of reference in which any psychotherapy may properly be critically evaluated. The following elements have been emphasized:

1. The theoretical understanding of human personality provided by dynamic psychology.

2. The clinical evaluation of each individual patient—the nature and intensity of his internal and external conflicts, the genetic history of those conflicts, his particular defenses against anxiety, his strengths as shown by past adaptations and achievements, his vulnerabilities and weaknesses as shown by the extent of his decompensation, his way of relating initially to the therapist, his intelligence and its possible impairments, the intactness of his concept formation, his loyalty to reality, his capacity for introspection and self-confrontation, and so on.

3. The utilization of psychotherapeutic techniques based on sufficient knowledge of dynamic psychology and applied appropriately to the individual case in the light of the clinical evaluation.

4. The personal qualifications and suitability of the psychotherapist, and, we may now add, his capacity to recognize and deal with transference manifestations in his patients and counter-transference tendencies in himself.

If these four criteria provide a valid frame of reference in which to evaluate psychotherapy, it is readily seen that those psychotherapists who have a fixed system of treatment for all patients who come to them are practicing poor psychotherapy. This is true whether it refers to those therapists who treat all patients with such banal exhortations as "Buck up," "Go home and forget it," "Stop worrying about that," "Pull yourself together," "Don't cross bridges until you come to them," and so on; to therapists who treat all patients by assigning reading for subsequent interview discussions in prepared booklets on how to live; to psychoanalysts who put all patients on the couch and tell them to free-associate; or to therapists who keep the syringe loaded with sodium pentothal for each patient, or who routinely start their hypnotic maneuvers promptly. One may give insulin to every diabetic, or operate every acute appendix, with, of course, some judgment as to dosage, timing, and collateral measures, but psychotherapy is, or should be, a highly individual matter for each patient. Far too often in current practice the type of psychotherapy used with the patient is determined solely by the limited training and ability of the psychotherapist rather than by either the type of illness the patient has or the type of patient that has the illness.

Of the various possible ways of classifying psychotherapeutic attempts, most psychiatrists would agree that two large groups could be identified—those which aim primarily at support of the patient, with suppression of his symptoms and his erupting psychological material, and those which aim primarily at expression. It is actually more appropriate to speak of a group of techniques utilized to accomplish suppression or expression than to speak of sub-groups of psychotherapies under each major heading. Suppressive or supportive psychotherapy, also called superficial psychotherapy, utilizes such devices as inspiration, reassurance, suggestion, persuasion, counselling, re-education, and the like and avoids investigative and exploratory measures. Such measures may be indicated, even though the psychotherapist is well trained and experienced in expressive techniques, where the clinical evaluation of the patient leads to the conclusion that he is too fragile psychologically to be tampered with, or too inflexible to be capable of real personality alteration, or too defensive to be able to achieve insight. Certain recovering schizophrenics or agitated depressions or children might illustrate the fragility, rigid character disorders, certain manics and hypo-

manics, and elderly patients might illustrate the inflexibility, and some paranoid states might illustrate the defensiveness. The decision to use suppressive measures is made actually because of contraindications to using exploratory devices. One can say, then, that supportive or suppressive psychotherapy, with its variety of techniques and devices for accomplishing support and suppression, is a valid psychotherapy provided it is applied on the basis of sound indications and not indiscriminately to all or most patients simply because the particular psychotherapist does not know how to do anything else with the patient, and provided the psychotherapist realizes that transference and countertransference manifestations can and do occur, and need to be handled, even in such superficial psychotherapy. Supportive psychotherapy may be brief or prolonged, as indicated, and may be carried out with individuals or with groups.

It is in the group of psychotherapies intended to be expressive that one encounters the various schools of thought, the adjunctive devices, the more frequent conflicts in theory, and the more significant question of personal suitability of the therapist. Expressive psychotherapies utilize such devices as exploratory probing through questioning, free-association, abreaction, confession, relating of dreams, catharsis, interpretation and the like, all with the purpose of uncovering and ventilating preconscious and unconscious pathogenic psychological material. Elements of support, reassurance, suggestion, advice, and direction are not necessarily excluded, and may, in fact, be consciously utilized. Expressive psychotherapy may be brief and intensive or prolonged, depending on the aims of the therapist and the response of the patient. Expressive psychotherapy is major psychotherapy and should not be undertaken without thorough grounding in dynamic psychology, adequate experience in clinical evaluation, practice under supervision, and personal suitability. Lacking this background, the psychotherapist is extremely likely to get into difficulties. He introduces topics for the patient to discuss without being aware that they are irrelevant to the matters pressing for expression within the patient, or that the patient cannot tackle a given topic until certain defenses are first pointed out and removed. He gives long and sententious theoretical explanations which he regards as interpretations, but which are either then learned as intellectual defenses by the patient or their content ignored while the patient basks in this verbal bath at the hands of the therapist. He permits himself unwittingly

to be drawn into an active role as an ally in the patient's external interpersonal struggles, while remaining oblivious to the provocative shenanigans of the patient which keep these struggles going on. He pounces on dreams or slips of the tongue with ready and pat interpretations which miss the point. He focusses his attention on symptoms, and tries to treat them by interpretation, or special investigatory questioning. He becomes embroiled in transference-countertransference jams and does not know how to extricate himself except by discontinuing the interviews for a while. I cite these common errors as illustrations of what may happen if the inadequately trained psychotherapist undertakes expressive psychotherapy. Needless to say such mishandling complicates the patient's illness exceedingly and renders more difficult the task of the inevitable subsequent psychotherapist.

Competent expressive psychotherapy may have goals which vary considerably. In cases where there has been an acute onset of neurotic symptoms in reaction to a discoverable precipitating event, and the patient's history shows a comparatively healthy course, the therapy may properly consist of thorough ventilation of the reaction to the upsetting event, with the therapist pointing out connections, relationships, and hidden motivations in the limited life area of the setting prior to the event, of the event itself, and of the patient's immediate and later reactions to the event. In skillful hands this is a most rewarding type of expressive psychotherapy. Recovery may be achieved in a very few interviews and the patient is restored to his previous good functioning with insights he would not otherwise have achieved. In such instances there is no therapeutic aim of exhaustive investigation, recovery of infantile memories, or altered ego structure. In other cases which may at first seem similar, the early clinical evaluation uncovers more neurotic difficulties than were at first apparent, and it becomes clear that the patient's adjustment prior to the precipitating event was a precarious one at best. The therapeutic aim may now change to one of more thoroughgoing alteration of the neurotic personality structure, and the expressive techniques lead into psychoanalysis. If the psychotherapist is competent to conduct psychoanalysis as well as the shorter expressive therapies with limited aim, he will have so handled the early therapy that the analytic techniques are a logical continuation of his early therapeutic work. If he is not so trained, he should at this point refer the patient to a suitable analyst.

Freudian psychoanalysis—and psychoanalysis actually implies “Freudian”—is a major, time consuming, and therefore expensive, type of psychotherapy. It is by no means a panacea, and its most competent practitioners would readily concede that as a method of therapy it has limited application in the vast field of human psychological distress. (As a dynamic psychology and as a method of investigation it is, of course, invaluable, and possesses almost unlimited applicability.) Its limitations as a method of therapy do not depend merely on such factors as its duration (twelve to eighteen months as a minimum; four to five years as a maximum), its cost to the patient, and the availability of analysts (approximately 500 in the United States, with one-fourth of these in New York City). There is also a considerable list of special indications and contraindications, as, for example:

1. The patient should be of at least bright normal intelligence on the Bellevue-Wechsler scale (115 to 120 IQ).
2. The suitable age range for adults is about 20 to 50, with certain exceptions to be made at either end of this range.
3. There must be some capacity for introspection, and some awareness of nuances of feeling in himself and in others.
4. There must be sufficient motivation in terms of initial distress and strong desire to change.
5. The patient must possess sufficient intactness of personality so that this intact portion may become allied with the analyst in the analytic work.
6. In general, patients with unalterable physical handicaps are not suitable subjects for psychoanalysis.
7. The general field for psychoanalytic therapy includes the psycho-neuroses, character disorders, some of the perversions, neurotic depressions, anxiety states, and some of the psychoses. Patients in the midst of acute external turmoil should not begin psychoanalysis as such until their life situations are more stable.

With all of its limitations, however, psychoanalytic therapy is, in well trained hands, a highly effective procedure for achieving in patients a profound alteration in their neurotic personality structure and developing otherwise latent potentialities for achievement and responsible living.

The Freudian school of psychoanalysis is the main stream of the psychoanalytic movement. There have, in the past, been several split-offs

from the main stream which resulted in transient and minor developments of non-Freudian schools. The school of the late Alfred Adler took one aspect of psychoanalysis, namely, the methods of the ego in dealing with external forces, and attempted to develop it into a system called individual psychology. The central theme of this psychology was that of inferiority feelings and the drive for power. This psychology and system of therapy died out with its leader. Carl Jung, also an early pupil and associate of Freud, split with him and developed a school of "analytical psychology" which emphasized symbolism and religious beliefs and which explained mental disorders, especially those of middle life and after, in terms of regressions to a collective unconscious, or racial heritage. His school still persists but his incorporation of Nazi racial ideology into his psychological theories has caused him to be severely criticized. The late Otto Rank, also an early pupil of Freud's, developed a system of therapy which emphasized the transference and the uncovering and working through of birth anxiety in a three months' period of treatment. There were many short Rankian analyses in the 1920's, but this system is now also extinct. The late Wilhelm Stekel, a remarkably intuitive man and a prolific writer, attracted a few followers to his technique of rapid and early deep interpretations of symbolic and unconscious meanings. His influence has now become almost nil. Karen Horney, originally a Freudian with many fine contributions to the literature, has led a movement in the last decade to eliminate a number of the fundamental concepts of psychoanalysis and to focus attention on current cultural conflicts as the main source of personality disorders. She rejects the libido theory, the significance of early psychosexual development, and in general takes a stand against genetic psychology in favor of culturalism.

There are other deviations from orthodox psychoanalytic techniques which are not represented by their practitioners nor regarded by others as separate dissident schools of psychoanalysis, but which are modifications of technique to meet the therapeutic problems in patients who are too ill to coöperate in the usual analytic procedure. These modifications are used chiefly with psychotics and involve approaches by the analyst which actively cultivate a treatment relationship, communication with the sick patient being established on whatever level is possible in the individual case. The success of such attempts depends on the resourcefulness of the analyst in coping with the patient's inaccessibility and his

capacity for empathy and intuition in understanding what is communicated by the patient's verbalizations, behavior, and attitudes. Long periods of careful therapeutic work are required but the results are often very rewarding. As the patient improves the treatment may merge into a more regular psychoanalytic procedure.

A special type of analytic psychotherapy developed by Rosen, for which the designation "direct psychoanalysis" has been made, deserves some comment. Rosen has reported a striking series of recoveries of severe and chronic schizophrenias. His method consists of repeated, prolonged sessions with the patient in which deep interpretative activity is carried out fearlessly and relentlessly. Interpretations are based on psychoanalytic theory, and sometimes on insights provided by other schizophrenics. The usual cautions and tentative approaches which have characterized others' work with psychotics are abandoned, and direct, deep interpretations are made promptly when the therapist believes he understands. The therapist also, when necessary to make contact, takes the roles of powerful figures in the patient's delusions and shouts denials, reassurances, and interpretations. Remarkable results are reported, and this work is now undergoing study under research conditions. It promises much but is at present difficult to evaluate.

The school of Adolf Meyer, identified as psychobiology, emphasized the sound concept of all-embracing study of man in his totality. He developed a new system of nomenclature which did not achieve significant acceptance, and termed his treatment "distributive analysis and synthesis." This psychotherapy aimed at exhaustive collecting of data regarding the patient's life, past and present, utilized diagrams to depict life influences, and assigned to the therapist the role of educator and explainer of the experiences and reactions in the patient's life. This procedure may be criticized as being far too theoretical and intellectual to influence many patients, and as having almost totally ignored the elements of transference and counter-transference in the relationship between therapist and patient. As a school of psychotherapy, it probably has a diminishing number of adherents.

All of the major psychotherapies—i.e., those which aim at significant alterations in personality structure rather than at symptomatic relief—have encountered the phenomenon discovered by Freud and termed by him "resistance." This refers to those partly conscious and partly unconscious tendencies in patients to resist self-knowledge and change.

as manifested in their inability to remember the past or to capture for therapeutic use the current unconscious content. Resistance produces a marked slowing down of progress, often approaching stalemate, while symptoms continue unaltered. Technical problems of resistance are among the most difficult to solve, and the long duration of major psychotherapy is attributable chiefly to this phenomenon.

In order to shorten the duration of therapy many attempts have been made to circumvent resistance. Chief among these techniques have been the use of hypnosis and certain sedative drugs. Under hypnosis or narcosis (also mild elation or light anesthesia) some patients are able to gain access to and to verbalize with affect otherwise unconscious memories, and to profit from the ventilation and abreaction and the interpretations of the therapist associated with this therapeutic experience. During World War II there was widespread use of intravenous sodium amytal and sodium pentothal as well as of hypnosis to produce dissolution of the resistance barriers against recalling overwhelming traumatic experiences. There often resulted clear recall and reliving of the traumatic experiences, with associated assimilation of the overstressful event and great diminution or relief of the symptoms. It was found that early treatment was essential, delay resulting in the building of stronger barriers against recall and fixing of the symptomatology, to which was then added the exploitation of secondary gains. These psychotherapeutic procedures had enormous significance in military psychiatry, but as sole treatment attempts, have proved to be disappointing in civilian psychiatry except with early traumatic neuroses in civil life. Such techniques of reducing resistance through hypnosis or narcosis do not constitute separate systems of psychotherapy, so that it is incorrect to speak of narcoanalysis, narcosynthesis, hypnotherapy, and hypnoanalysis as psychotherapies. They are adjuvant techniques to be used as a preliminary step in overcoming an initial impasse, or as devices to be introduced during psychotherapy when strong resistance blocks further progress.

The attempts to shorten the duration of psychotherapy have led to other techniques which make use of psychoanalytic principles but which try to achieve faster results especially through manipulation of the transference, role-taking by the therapist in order to provide a corrective emotional experience, and interruptions of treatment to avoid a difficult dependent transference. Alexander, French and others who report this work maintain that their therapy is entitled to be called psychoanalysis—

psychoanalysis with more flexible utilization of techniques. Many critics insist that the techniques as reported represent abandonment of fundamental analytic principles and that the goals of such therapy have become relief of symptoms and conventional social adaptation instead of the goals of structural personality alterations of psychoanalysis. Many other studies of short psychotherapy using psychoanalytic principles have been reported in the literature, and it seems well established that the whole field of psychotherapy has been greatly enriched by contributions from psychoanalysis.

In the last analysis there is only one psychotherapy, with many techniques. This one psychotherapy must rest on a basic science of dynamic psychology, and those techniques should be used which are clinically indicated for each individual patient—certain appropriate techniques for the initial stages and others later as the continuous clinical evaluation proceeds *pari passu* with therapy, and the goals and potentialities for the patient become more clearly delineated through his responses to therapy. And, finally, it is important to recognize that techniques as such are hardly separable from the individual who uses them. Psychotherapy is an enormously complex intercommunication and emotional interaction between two individuals, one of whom seeks help from the other. What is done and said by the one who tries to give help is inevitably his personal version of technique. Beyond all knowledge of dynamic psychology and training in techniques is his own individual personality, with its inevitable variables as to sex, physical appearance, depth of understanding, ability to communicate ideas, tone of voice, set of values, and all of the other highly individual elements which differentiate one therapist from another. The utmost impersonality and analytic incognito cannot exclude the effect of such individual elements. Hence we may say that in addition to a critique of psychotherapy one must also make a critique of the psychotherapist.

SAFEGUARDS IN THE USE OF
NEW DRUGS*

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URING THE last five decades the life span of man has been increased from 49 years to 67 years. In other words, in half a century man's life has been increased almost 37 per cent.

There are several reasons for the lengthening of the life span. Most of them are well known to all who are interested in the preservation of health and the treatment of illness, as they include such familiar topics as improved medical education, improved hospital facilities, improved sanitation, education of the general population to beneficial health practices, widening of the surgical horizon, development of physical medicine, and more effective drug measures. The latter phase, of course, is among the best known as it has offered truly remarkable life-saving techniques and, as a result, has fired the imagination of everyone. "Miracle drugs" are the order of the day. Surgery and rehabilitation, for example, also have inspired new hope for the medical profession and countless suffering patients, but many of the latter remember only the "sulfa" drugs and penicillin, and ask almost daily, "What's the latest cure?"

Obviously, perplexing problems arise as stories of the newer agents are circulated. At the same time many questions are raised: Is the new drug only ready for experimental use in humans, or is it suited to general use? Does it have harmful possibilities? Will it replace or merely supplement other treatments? Will it be of lasting importance? And, inevitably, can it be used for self-medication?

Such questions often cannot be answered completely for a long time after the drug has been introduced into use. However, it is customary today, in fact, obligatory, to collect more revealing data than were sought and reported a few decades ago. Not only is there a keener

* Given October 4, 1948 before the 21st Graduate Fortnight of The New York Academy of Medicine.

appreciation of the need for such data by the manufacturer, as well as the researcher and prescriber, but there is a law that exerts considerable regulation over new drugs introduced into interstate commerce. Other factors likewise exert influence over the use of drugs so that the accumulation of scientific data that now appears in published literature is sometimes almost overwhelming. Unfortunately, not all of the published reports are entirely dependable: Errors in work may be reported; erroneous interpretations may be drawn; and enthusiasm or wishful thinking may creep into the conclusions.

Thus, there is need for constant screening of scientific findings to weed out the undesirable, catalogue the desirable, question the doubtful, and sort for intelligent use that which is immediately applicable. Several agencies and scientific bodies undertake these responsibilities and serve as "medical watchdogs," their work providing a protective bulwark against, among other things, charlatanism and pseudo-science, and, at the same time, encouraging sound research and rational therapeutics.

Among the well-known agencies with legal backing is the Food and Drug Administration, popularly known as the F.D.A. This agency has its headquarters in Washington and offices throughout the country; about 1,000 individuals, professionally trained and others, make up its personnel. Its influence on therapeutics is seldom realized by those in practice unless they are doing research with new drugs. But this influence is important; in fact, amazingly important when one considers that the Federal Food, Drug and Cosmetic Act became effective only in October, 1940. Covering foods, drugs, cosmetics, and devices, the Act has implemented many changes in drug industry practices, in health standards, and in providing protection for the public. It also affects the drugs prescribed by physicians, a fact that cannot be ignored, although it is often overlooked.

Briefly epitomized, the Act demands the testing of all new drugs before they are placed in interstate commerce to determine their safety when used as directed; that all labeling be truthful and properly informative; and that the drugs be manufactured so that they are satisfactorily pure and subjected to adequate controls during manufacturing processes. This has resulted in at least proving the safety of drugs, when used as directed, before they are marketed. Indirectly, it also has served as a tremendous stimulus to the development of data to substantiate proposed advertising claims. It is obvious, however, that there are still innumerable

claims offered for many products that require further proof before they can be accepted generally. This is due, in part, to the limitations of the Act, which was passed by Congress to make self-medication safe, not to instruct physicians in the use of drugs. Nevertheless, the wording of the provisions of the Act and some Court decisions are sufficiently broad to permit the exercise of considerable influence by the Administration also on promotional material and labeling directed to the medical profession; drug manufacturers, if no one else, will attest to this.

There are some criticisms directed against any efforts of the Food and Drug Administration to permit the marketing of only therapeutically useful products, an objective with which many may sympathize, but which is regarded as a dangerous precedent by others. Most of the sincere critics claim that such rulings or decisions from the Administration, in effect, are equivalent to attempts to regulate the practice of medicine. These critics admit that fraudulent preparations should be removed without any hesitancy, but they stoutly deny that the Federal Act permits any governmental agency to force manufacturers or pharmacists, for example, to place on labels warnings such as the one required for thiouracil, or, in effect, to prohibit the sale of certain glandular substances that the Administration recently has claimed to be inert and therefore open to suspicion. The critics claim that the physician should have the sole right to decide what he is to administer, even giving, if he wishes, what may amount therapeutically only to placebos.

Where these differences of opinion may end is uncertain at the moment. Undoubtedly, however, the major questions that are involved are far from settled. There is much to be said for those who argue that prescription items are essentially the responsibility of the medical profession, but it cannot be overlooked that the Food and Drug Administration, nevertheless, has been determining what *is* a prescription item and what is an "over-the-counter" product. On the other hand, there is also much to be said for efforts that are intended to provide the optimum of protection for those who have a legitimate interest in drugs.

At least one other point concerning prescriptions should be emphasized in this discussion on safeguards in the use of new drugs. Until the Federal Food, Drug and Cosmetic Act became effective most drugs in interstate commerce, for all practical purposes, could be purchased freely without prescriptions and without violation of a law—except, of course, narcotics. With the enforcement of the Act, many drugs were

listed for prescription use only, and no patient could honestly secure such a drug without a prescription. This caused, and still causes, considerable confusion for the patient who blithely asks for whatever he wants, and for the physician who tells his patient to get "so-and-so" at the pharmacy but neglects to write a prescription for the order. Considerable embarrassment has arisen over this problem. For those who are in doubt as to whether a product is restricted to prescription use, a call directed to a pharmacy will elicit information concerning the legal status of a drug. Furthermore, if there appears on a drug label a statement to the effect that the drug can be dispensed only on the prescription of a physician or dentist, the remedy cannot be released by the pharmacist without the necessary order; to do otherwise makes him liable for prosecution.

It is interesting and important for physicians who do their own dispensing to recognize that they too are required by law to observe the provisions of the Federal Act just as are pharmacists when they fill prescription orders. Thus, the dispensing physician must observe in detail regulations concerning adequate directions for use, warnings, and other pertinent information.

And finally, so far as the Federal Food, Drug and Cosmetic Act is concerned, drugs that are available solely for investigational use can be obtained only upon filling out special forms supplied presumably only to qualified investigators. Thus, theoretically at least, drugs still in the stage of experimental investigation and not yet available in commerce can be used only for research purposes. Unfortunately, when stories appear concerning some new treatment for a serious disease, pleas from patients may force premature use of the treatment, which could have disastrous results if a toxic drug were placed in inexperienced hands. This regulatory safeguard for new drugs is intended to ensure the collection of adequate data before a new drug is placed in interstate commerce, and to prevent its misuse.

In addition to the Federal law just discussed, there are a number of state laws of somewhat similar pattern that place restrictions on the unwise use of drugs. Familiarity with such laws must be gained by physicians according to the states in which they are located. A few communities also are well-known for their regulatory protective activities, New York City being an outstanding example.

The National Institute of Health (N.I.H.) is another agency that

plays a part in the control of therapeutic agents by operating under a Federal Act which permits it to assume a supervisory role over biologic and arsphenamine preparations. Such drugs normally do not come within the activities of the Food and Drug Administration, although there are times when both organizations exercise a mutual interest. A biologic preparation such as a vaccine or toxoid must come from a producer that holds a license issued only after his place of manufacture has been inspected. The license is renewed each year. Like other drug manufacturers, the biologic manufacturer is subject to periodic plant inspections and his product may be examined at any time on the open market.

The Federal Trade Commission (F.T.C.) does not influence directly the physician's prescribing habits. This agency is concerned primarily with products sold to the public, although obviously there are some preparations that may be promoted to the public and also to the medical profession, for example, mineral oil. This agency is not concerned with labeling—which comes within the purview of the Food and Drug Administration—but with what is known as collateral advertising and which includes advertisements appearing in books, newspapers, over the radio, and in other media. It initiates action by its staff which scrutinizes advertising material and through complaints submitted by various interested parties. Some idea of its work can be gained from a study of its continuing survey of radio and periodical advertising to detect advertisements that may be false or misleading. During 1947 there were examined 412,950 newspaper and other periodical advertisements and 641,402 radio commercial continuities, of which 55.8 per cent pertained to drugs, 16.9 per cent to cosmetics, and 5.9 per cent to food.

So far this discussion has been confined to regulatory bodies that have the backing of the Courts for enforcement of the Acts under which they operate. There are, however, several agencies that have no legal support as we normally view it and yet which exert considerable influence, directly or indirectly, on health practices. One such agency is the community Better Business Bureau which consists of civic-minded and business-wise individuals who undertake a self-policing task, among other things, to assure truthful advertising for the community and to draw attention to harmful health practices and charlatans. Obviously, the Bureau has no close relation to the promotion of the so-called ethical drugs or to the activities of those who honestly attempt to follow their chosen professional careers; but, on the other hand, it does serve as a

useful ally to the physician by offering another shield of protection for the medically untrained individual who persists in looking for miracle cures.

The other agencies that now may be discussed are part of the American Medical Association and are included in a unit of the Association known as the Division of Therapy and Research, a unit which requires approximately sixty professionally trained and other individuals at headquarters office to expedite its work and otherwise to serve the medical profession. Included in the Division are the Council on Pharmacy and Chemistry, Council on Foods and Nutrition, Council on Physical Medicine, Bureau of Investigation, Laboratory, and the recently formed Joint Committee on Cosmetics. The latter office is so new, in fact, that the Committee held its first meeting on October 12, 1948. Another committee that is now in the process of organization, and hence, details are lacking at this time, is one that will be concerned with toxicologic problems facing the medical profession and the general population. One of the problems that the committee will explore early is related to the use of pesticides which has created serious hazards that are causing much concern to the Councils on Pharmacy and Chemistry and Foods and Nutrition, and to other agencies.

This audience needs no introduction to the work of the aforementioned A.M.A. agencies. However, in view of the intended purpose of this paper, i.e., a discussion of the safeguards in the use of new drugs, a few words concerning each office are not inappropriate as they will serve, like the preceding comments, to introduce the final part of this discussion which will relate solely to the use of new drugs.

The Council on Pharmacy and Chemistry was organized in 1905 as a standing committee of the Board of Trustees of the American Medical Association. Operating under seven basic rules, it evaluates new drugs and reevaluates the older remedies, making available its findings in published reports in *The Journal of the American Medical Association*, in *New and Nonofficial Remedies*, and in several other books such as *Glandular Physiology and Therapy*, *Useful Drugs*, and the *Epitome of the United States Pharmacopeia and National Formulary*. In addition, the Council answers thousands of inquiries each year, makes available exhibits for medical and health meetings and, of considerable importance to research workers, makes available modest grants-in-aid through its Committee on Therapeutic Research, and stimulates research

through its Therapeutic Trials Committee. The interest of the latter committee in the study of the effect of endocrines on cancer has been reported in *The Journal of the American Medical Association* and is well known; it needs no detailed explanation at this time. Through advice to those responsible for the acceptance of advertisements in A.M.A. publications and other journals that follow Council policies, such as most state medical journals, and because many purchasing departments in hospitals and other organizations are influenced by "Council acceptance" in the purchase of their supplies, there is considerable stimulation to drug manufacturers to prove their claims and the safety of their products if they contemplate seeking the Council seal.

The other Councils follow a somewhat similar but more restricted pattern in scope of activities, but the rules under which they operate in their acceptance programs are essentially the same. The Joint Committee on Cosmetics has been established because of the many problems associated with the use of cosmetics and it already has compiled an impressive amount of data. Except to again point out that all of the Councils and Committees welcome inquiries, these bodies now can be dismissed to permit passing to the actual development and use of new drugs. No attempt can be made to be comprehensive, but there are certain phases that are the source of continuous interest and study and therefore merit special attention.

The rapidity with which chemotherapy has advanced in the past ten years has been faster, probably, than the mind often has been able to grasp. Unless careful thought is given to the specific developments, the newer ideas are regarded sometimes in the same light as the older and less effective remedies. In addition, the enthusiasm observed in the first wave of encouragement for a new drug may be so extensive that prescribers are led to believe that the drug has no limitations. Thus, practically overnight the sulfonamides and antibiotics were introduced into medical practice and accepted so promptly that their limitations were sometimes overlooked by their less critical users. On the other hand, these agents sometimes were not used to their fullest extent because of lack of knowledge or even indifference to the facts that were available. While such drugs have saved countless lives, they can be most effective only when used properly.

There are, however, many drugs that are not as harmless as the sulfonamides and antibiotics—and certainly no one can claim that these

drugs are without harmful possibilities in view of the incidence of reactions that follow their use. But there are other drugs that produce even more striking side-effects. And, of course, there also are those drugs that are known to be inherently toxic in the majority of individuals and whose toxicity is not related to individual sensitivity, but which are used, nevertheless, because their beneficial possibilities outweigh their harmful possibilities. Today, the variety of therapeutic agents subject to the command of the physician are so varied as to be truly amazing when they are compared to the remedies of a few decades ago, but at the same time their use presents new problems.

In view of recent developments in chemotherapy—and here the word chemotherapy is not used in the restricted sense as was done by Ehrlich, i.e., the use of drugs to combat an invader, but in the more general and popular vein to embrace pure substances prepared for specific attack against disease—it is not surprising to find considerable confusion when a new drug makes its appearance on the market. Even the most conservative promotional material bears an air of optimism that is misleading unless the statements are critically examined. Even then, the opinions of the experts often must be sought to bring some semblance of orderly thinking and prescribing. And when an agent is proposed for a disease such as cancer, hypertension, virus infections, or some other equally disturbing malady, the pressure from patients and relatives to use the new “cure” provides an additional complication.

It becomes necessary, then, for the physician sometimes to go beyond the safeguards set forth for new drugs by the agencies described earlier in this paper; he can obtain information at any time from offices such as the Council on Pharmacy and Chemistry, but often he will find it expedient to ask certain searching questions to determine to his own satisfaction if the new product is all that it is claimed to be. For example, he will be more content if he knows that dependable studies on biochemistry, pharmacodynamics, functional pathology, acute and chronic toxicity and adequate clinical trials are available. Then he may care to ask:

For what conditions is the drug effective?

How effective is it in these conditions?

Is it superior to other drugs and methods of treatment?

What is its inherent toxicity?

Does the toxicity outweigh the therapeutic advantages, keeping in

mind the seriousness of the conditions for which it is being offered?

If there are other drugs equally or more effective in the same conditions, does the new drug offer any advantage?

Are its applications limited? If so, how?

How can its usefulness be properly controlled?

The changing trends in therapeutics make it even more important for the physician to be constantly on the alert for new drugs and new ideas. No sooner has he learned to use a drug than another is offered to take its place. Only a few years ago, for example, Dakin's solution, iodine, mercurials, and dyes were the popular agents for the prevention and treatment of infections. Today, the sulfonamides, penicillin, streptomycin, and other antibiotics are the drugs most commonly used for infectious processes. Locally applied agents now include anionic and cationic detergents. A few years ago quinine was about the only remedy for malaria, but today it is being supplanted by other more effective and less distressing substances. A few years ago, morphine and codeine were the only potent analgetics, but today the situation is entirely different. Antihistaminics were practically unheard of a few years ago, but now they are appearing almost faster than they can be catalogued.

Such a list of agents could be lengthened by the addition of vitamins, hormones, anesthetics, anti-convulsants, diagnostics, lipotropics, amino acids, blood derivatives, detoxicants, scabicides, and vaccines, but they would only serve to emphasize what is generally familiar, namely, therapeutics is not static. Furthermore, some of the more widely accepted concepts become less popular as experience and knowledge are gained. For example, sulfathiazole and sulfapyridine are no longer in New and Non-official Remedies because of their high incidence of reactions; the topical use of sulfonamides has been condemned repeatedly because the incident toxic reactions far outweigh any beneficial results; the combined typhoid-paratyphoid vaccine has been omitted from New and Non-official Remedies because of the toxic reactions from the paratyphoid fraction; pentnucleotide has been replaced by penicillin in the treatment of agranulocytosis; thyroxin has been omitted from N.N.R.; and propylthiouracil has replaced thiouracil. Other examples could be cited but they obviously are not necessary.

As the newer drugs are developed, and as their potency is increased, it may be necessary to regulate dosage by every means available includ-

ing the determination of the drug in blood levels, urinary excretions, salivary excretions, and by other means. These laboratory procedures are often important if reactions are to be kept to a minimum and therapeutic response to a maximum.

It is impossible to include in one paper all of the phases attendant to the proper use of drugs. No one can deny, however, that many accidents have occurred because drugs were not properly tested or their actions thoroughly understood before they were used. Safeguards intended to prevent such reactions have been devised with governmental backing and from voluntary sources, but the final safeguards lie with the physician who uses a new remedy. It is up to him to exercise individual judgment, based on a careful study of the available data, when a patient is undergoing treatment. Failure to do otherwise may, in fact, be inevitably certain to, provoke unfortunate consequences.

MEDICINE UNDER HITLER *

GEORGE ROSEN

THE historian of recent German medicine who approaches his subject under the impression that he is dealing with a radically new and unique phenomenon soon finds it difficult to draw any sharp line distinguishing the influence of National Socialism from deep-seated tendencies in the broader tradition of German culture. Broad strata of the population, including a considerable sector of the intellectuals, were emotionally predisposed to the kind of system Hitler offered. The acceptance and exaltation of the Third Reich by the medical profession cannot be fully appreciated without an awareness of psychological factors and sociological trends that conditioned this group.

Essentially a section of the middle classes, the medical profession experienced the same social and economic changes that affected other middle class groups. At the beginning of the twentieth century there was still a well-defined social order in Germany. Vocational groups were clearly differentiated by their status in society. Academic training was highly regarded and carried with it considerable social prestige. The natural sciences were likewise highly esteemed. In this social order the physician as a university graduate, a representative of a liberal profession, and as a natural scientist, held a secure position. During the past forty years, however, society has been subjected to a profound transformation that still continues. War and revolution came and went. Government entered more and more into the sphere of individual action. Natural science no longer enjoyed the unquestioning adulation which had formerly been its due. Currents of thought and action that were regarded as forever banished rose from the depths and began to unfold their baneful energies. Naturally, the medical profession could not remain unaffected by these changes.

Germany in the decade following World War I exhibited most clearly and most acutely the general lack of direction characteristic of modern Western society. Widening opportunity for social advancement

* Presented before the Section on Historical and Cultural Medicine of The New York Academy of Medicine, 12 November, 1947.

through education was accompanied by the negative phenomenon of the intellectual *déclassé*. Increasing bureaucratization and integration of professional activity generated resentment and a nostalgic yearning for the good old days of individualism. These dissatisfactions expressed themselves in mystical philosophies of politics and science. In a world of industrialism and capitalism, dreams of German greatness, heroic leaders and a revival of an idealized Reich provided a hope of escape for those who rejected more realistic solutions of their problems. The philosophical materialism that had dominated scientific medicine was deprecated and replaced by the romantic and mystical ideologies of Neo-Hippocratism, Neo-Paracelsism and Neo-Vitalism. This wave of mysticism which engulfed Germany prepared the way for Hitlerism and its absurd dogmas. It was a social situation that demanded charismatic leadership.

Upon Hitler's accession to power, steps were undertaken to co-ordinate and to subordinate medicine in all its aspects to the larger purposes of the National Socialist state. Medicine became an instrument of fascist domestic and foreign policy. The official position was expressed by Reiter, President of the Reich Health Office, in the statement: "The physician fights as a biological soldier for the health of his people."

To assure a medical service obedient to the state, the medical profession was reorganized in conformity with the leadership principle and the concept of the Aryan race, those two ideological cornerstones of the Third Reich. Under the Weimar Republic the interests of the profession were represented by the *Aerztekammern*, chambers of physicians chosen by all qualified practitioners of a regime, which supervised the conduct of their members. The economic interests of insurance doctors were represented by two great associations, the *Hartmannbund* and the *Aerztevereinsbund*. Following the seizure of power, all the former medical chambers were dissolved and replaced by a new hierarchy, headed by the *Reichsärzteführer*, the physicians' leader appointed by Hitler. The *Reichsärzteführer* represented the peak of a hierarchical pyramid with the absolute right to appoint and dismiss his immediate subordinates, and each of these in turn had similar rights until the base of the pyramid was reached. The Leader of the physicians was the head of the *Reichsärztekammer* (Reich Chamber of Physicians), the state medical organization which had jurisdiction over

the licensing of physicians to practice and therewith controlled professional activity. Its decrees were enforced by the *Deutscher Aerztegerichtshof* (German Court for Physicians) operating at the district level. Physicians already engaged in insurance practice or wishing to enter such practice were kept in line by the *Kassenaerztliche Vereinigung Deutschlands* (Association of Sickness Insurance Doctors of Germany). This organization regulated admission to insurance practice and administered decrees which applied to insurance practitioners.

Every phase of a physician's professional activity was minutely regulated, and it was expected that the physician would accept and further the principles of National Socialism. Recalcitrance carried economic penalties such as loss of official position and license to practice. Behind these loomed the jail and the concentration camp.

Further to assure that the primary obligation of the medical profession would be to the State, medical training provided indoctrination in party dogma. Prior to 1933 medical education had been of high caliber, but thereafter the medical curriculum was thoroughly standardized and Nazified. Two courses, one on racial hygiene, the other on human heredity, were introduced into the curriculum of every medical faculty. In addition, all other medical courses were supposed to stress the superiority of Nordic man, and to be aimed at the definite objective of creating good Nazi leaders.

In a like spirit medical research was directed toward the justification of National Socialist racial doctrine. Before the advent of Hitlerism, Germany's many research institutes enjoyed world-wide renown. In 1933, most of these institutes, especially those engaged in research on subjects having a social aspect, such as hygiene and psychiatry, were coördinated with Nazi political purposes, Nazi personnel was added, and politically suspect scientists were removed from their posts. In general, institutes and faculties concerned with any aspect of social hygiene, or with the medical phases of geopolitics, were under National Socialist leadership and influence.

In the field of public health, services which existed before 1933 were similarly subverted to National Socialist policy by drastic coördination of administration and function. This administrative reorganization was accomplished by a significant shift in emphasis. Under the Weimar Republic, the preventive aspects of public health work were stressed, but under Hitler the protection of the racial inheritance be-

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE



MARCH 1949

PRESIDENTIAL ADDRESS *

BENJAMIN P. WATSON

President, The New York Academy of Medicine

FELLOWS of The New York Academy of Medicine: I thank you for the great honor you have conferred upon me in electing me your President. I accept office with very mixed feelings: First, there is that of intense pride that you should have considered me worthy, but there are also those of deep doubt and misgiving as to my ability to give the standard of service expected of me and set by my predecessors. I can only pledge you my utmost effort.

Fortunately, while the Presidency changes every two years, the Trustees, the Council, our great Committees of Library, of Public Health Relations, of Medical Education and of Medical Information have continuity of Service.

It is to the Chairmen, members and permanent officials of these and of the other Committees that I shall turn for information and enlightenment. There is also immeasurable satisfaction in the knowledge that we have in our Director, Dr. Howard Reid Craig, an able and devoted administrator.

With all of these to guide me and through my contacts with individual Fellows I hope that I shall reflect in everything I may be called

* Given January 6, 1949 at the Annual Meeting of The New York Academy of Medicine.

upon to do or say, the considered judgment of the whole body of the Fellowship.

It is perhaps not inappropriate that one who has spent a large part of his professional life as a teacher should occupy this position, for the Academy is first and foremost an educational institution. It concerns itself with maintaining and raising the standards of undergraduate and graduate training. Through the meetings of its several Sections it provides forums where every advance in medicine in all of its branches can be discussed. It brings to New York authorities from all over the country and abroad who in the Friday afternoon lectures and in the Sectional and Stated Meetings, give first hand information on subjects on which they are at work. All of its meetings are open meetings so that it makes available to the whole medical profession a continuing post-graduate education.

Through its Committee on Medical Information it provides annually a series of Lectures to the Laity for the information and instruction of the lay public in things pertaining to medicine and problems of health. It stands ready to interpret for press, radio and screen current news on everything relating to the healing art to the end that their releases be informative and instructive, and at the same time not misleading.

Through its Public Health Relations Committee, which includes Fellows representing every branch of medicine, it conducts detailed investigations on matters pertaining to community and national health. Some of these studies are initiated by the Academy itself, but many are brought to it by Boards of Health and other organizations. When the committee undertakes such studies it does so in the most detailed and thorough fashion, inviting to serve with it and bringing before it authorities from all over the country, representing every phase of the problem presented. The financing of this work is frequently helped or entirely provided for by one or more of our great educational foundations. Thus the facts on which to base the final reports are as complete as it is possible to make them, and the reports themselves are free from preconceived ideas and of bias. It is this objectivity of approach which has given to the Academy the honored position it holds today in the councils of our city and of the nation.

Our greatest asset is the Library, which in point of numbers of books and manuscripts is second only to the Surgeon General's Library in Washington. Here, accessible not only to the Fellows but to the

public at large are to be found current periodicals, text books and monographs, and also a rare collection of medical classics in book and manuscript form from which the whole history of medicine can be studied at first hand.

In human affairs no intelligent appraisal of the present and no forecast of the future can be made or planning done without a knowledge of the past. This perhaps is especially true of medicine in which all progress has been the result of a slow process of evolution, each age seizing upon new facts as they emerged and applying them to the teaching and practice of the time, while discarding all that was proven to be faulty and worthless.

One sometimes hears it stated, usually by those with some ulterior motive, that medicine has become much too scientific and that we ought to return to the simpler methods and practices of a bygone day. But the scientific approach to medicine is not a thing of recent date. It stretches back to the beginnings of recorded time. In the Egyptian Papyrus dating back three to four thousand years recently gifted to the Academy, there are precise and detailed descriptions of diseased states, all founded upon accurate, that is to say, scientific observations. The dictionary definition of science is "knowledge gained by observation, experiment and reasoning, knowledge coördinated, arranged and systematised." The word scientific connotes something "concerned with the acquisition of accurate and systematic knowledge of principles by observation and deduction." So long as work has been done within the framework of these definitions advance has been made. When men forgot them or were hampered or prevented from applying them by outside pressure, progress ceased.

Science really began with the ancient physicians. Huxley in an address delivered in the year 1874 said: "In the days when all the innumerable applications of physical science to practical purposes were non-existent even in dreams—what little physical science would be seen to bear directly upon human life lay within the province of medicine. Medicine was the foster mother of chemistry because it had to do with the preparation of drugs and the detection of poisons, of botany because it enabled the physician to recognize medicinal herbs, of comparative anatomy and physiology because the man who studied human anatomy and physiology for purely practical purposes was led to extend his studies to the rest of the animal world. The medical school furnished

the only regular training for the naturalist, whilst he found the medical profession the likeliest means of earning his bread." And now medicine becomes ever more and more in debt to the pure scientist.

There have always been engaged in the healing art those who were imbued with the true scientific spirit, men capable, as Sir James Paget put it, of "taking notice of all conditions in which objects or events are found, their concurrencies, their seeming mutual relations, all their variations." It is to such men working all through the ages with the means available to them that medicine owes its present status.

The true research worker is a rarity; his joy in life does not derive from applying, even in the most perfect manner old and tried methods; he is constantly under an imperative urge to range wide and far in an effort to find new truths and new correlations of facts. What remains for the rest of us is to determine which of these can be put to practical use. Within our profession, as in every other walk of life, there are those who resist change—the reactionaries so called. They are so set in their ways that they react against any innovation and refuse to accept it. At the other extreme are those who look too quickly for the practical application of every new scientific discovery and so frequently bring disillusionment and disappointment to themselves, to their patients and to the public.

There are many examples in medical history of these two extremes. One has only to cite the opposition within the profession to Jenner's vaccination against smallpox; the obloquy heaped upon Semmelweis for the publication of his facts regarding puerperal fever; the resistance encountered by Lister to his demonstration of the role of micro-organisms in surgical sepsis, the violent reaction against Simpson's advocacy of general anesthesia in labor, and even in our time the reaction against the Maternal Mortality report of this Academy, a reaction which happily was very short lived.

The rush of the optimists to put to clinical application every scientific discovery as soon as it is announced is a phenomenon of more recent times. It is partly the result of the rapid dissemination of "news" in the medical and lay press. Such a tendency may be just as retarding to orderly progress as stubborn opposition to change.

Fortunately, between these two extremes there is the great body of medical men conditioned by their training to await the conclusions arrived at by those capable of reviewing the facts, repeating the experi-

ments and conducting clinical research. These are the men who constitute the backbone of the profession, bringing to their individual patients and to the community all the best that contemporary knowledge has to offer.

It is to this play and interplay between the research workers, the reactionaries, the impatient enthusiasts and the steady thinkers, that we owe our present position in medicine. That position has been arrived at by a slow process of evolution, one development following on the other in orderly sequence. There have been times when progress has been slow and times, as in recent years, when the pace has been accelerated, but always there has been advance.

In contrast to this let us glance back in history and find what happened when there were exerted influences and forces outside of medicine; forces not directed by the scientific spirit, but by superstition, dogma, or political ideology.

The ancient Egyptians, as we have seen, had the true scientific approach, but they made no real advance in medical knowledge. No progress was made until taboos on human dissection were lifted in the fourth century before Christ; then there was founded the great School of Medicine in Alexandria, which for the next four or five centuries became a seat of medical learning for the whole middle and Eastern Mediterranean area. In the second Century A.D. when Galen studied there, dissection and the teaching of anatomy from the cadaver had again been suspended, so the only material available to him were human skeletons preserved in the museum and the Hippocratic writings and the anatomical teachings of Herophilus preserved in the library. In Rome, to which Galen returned to practice medicine, there was strict interdiction of human dissection imposed by the State. So it was inevitable that in the sixteen books on human anatomy which Galen subsequently compiled there was much error. These treatises and the other writings of Galen founded upon them remained the sole and only authority until the sixteenth century when the world emerged from its thousand years of darkness. During that time medicine made no progress for, says McMurrick, "the study of anatomy became conventionalized into the reading of a translation in Latin of an imperfect summary by an Arab of Galen's teaching—Ignorance of the original treatises concealed the fact that Galen's contributions to Anatomy were based on dissections of animals, chiefly monkeys, that his anatomy was not in reality human

anatomy." Galen's writings were not founded upon objective observations. They were nothing more than "dogmatic expositions."

With the dawn of the New Age in Europe there came again the urge to seek after anatomical truth but now the ban of the Christian Church had been put upon human dissection. The story of how the fathers of anatomy, among them Leonardo da Vinci, Vesalius and Servetus defied that ban and suffered as a result is familiar to all of you. But their sacrifice was not in vain for it was under their successors in Padua that Harvey studied the anatomy of the human heart, and so laid the foundation for his treatise on the circulation of the blood, which remains today the model of all that a scientific treatise ought to be. Its publication marks the turning point in modern medicine.

It would seem a far cry from the seventeenth century to today did we not see again a great State putting an interdiction on the search for scientific truth, did we not have in our own land organizations, made up of sincere, though we think, prejudiced and deluded individuals, which seek to limit our methods of research. And now there is the threat of governmental bureaucratic administration of the practice of medicine, a threat we believe, which if carried into effect will retard and may well for an indefinite time stop the normal evolutionary development of medical science.

The Academy is concerned with maintaining and raising the standards of medical teaching and practice. We feel, and I know that the feeling is shared by the great majority of our Fellows, that any plan of compulsory National Health Insurance which could be put into effect at the present time would result in a general lowering of the quality of medical care and would put upon the individual doctor a task which he could not perform with any satisfaction to himself or his patients.

The day is over when medicine can be practiced by the doctor who carried all of his equipment in a little black bag. If he is to use all the diagnostic and therapeutic aids now available to him—and to do less would be analogous to an early twentieth century physician practicing without a thermometer or a stethoscope—if he is to use modern methods he must have access to all sorts of laboratory service, to radiological service; he requires the aid of nurses and of technicians. He must be able to hospitalize his patient and call on specialist advice when necessary. All of this is being done in hospital and in private practice today. Doctors are combining into groups each having within it individual spe-

cialists; there is a pooling of equipment and of technical personnel and so a reduction in overhead expense and as a result reduced cost to the patient. The major cost of medical care today is not represented by doctors' fees but by these ancillary services which are necessary if the doctor is to give to his patients all that modern science has made available for them. To meet this cost voluntary insurance for all of these services has been made available. These plans are gradually extending and developing, taking in more and more of the population. They will develop further by the process of natural growth and evolution. They are the outcome of the work and thought of that great body of the medical profession to which reference has been made. The good results achieved in medical research, in medical teaching and in medical care, all carried on by the profession without bureaucratic control, are evidenced by the fact that this country is now the Mecca for medical pilgrims from all over the world, that its standard of national health is high and its mortality rate low as compared with other countries, and that life expectancy is steadily increasing.

The intervention of government in the manner now contemplated and at this stage might be likened to the impetuosity and impatience of the doctor who, with his patient doing well, insists on applying some new therapeutic agent the merits of which have not been fully proven. There is, however, this difference, that whereas the medical enthusiast can withdraw his therapy and his patient recover, governmental action will be irrevocable and may be permanently disabling.

This Academy in its report on "Medicine in the Changing Order" has placed itself on record as recognizing the need for improvement in the distribution of medical care so that it may become available to all but it pleads for continuing study and development. There may then emerge a system which will make possible the rendering of the highest quality of medical service to every individual and to the community and at the same time the continuance and encouragement of research and the betterment of teaching.

The training required to equip a doctor to give what we regard today as adequate medical care is long and arduous. All who are engaged in medical education are giving constant thought to ways in which that training may be improved and better adapted to the ever-changing needs of the day.

Something that gives great concern is the length of time necessary

to equip a doctor to practice his profession—four years in college, four years in medical school and if he is to qualify for one of the specialties, five years or more of internship and residency. He is well over thirty years of age before he is ready to go out into the world and begin to earn his bread.

It seems impossible to shorten the undergraduate course of four years, for in that time his teachers have to interpret for the student all that remains worthwhile from the past and all of contemporary knowledge and to do it in such a way as to enable him to contribute to or at least to keep pace with the advances of the future. This means that he must be given certain disciplines which will inculcate into him the scientific approach as we have defined it. In my student days the chief discipline was the study of gross anatomy; now in addition there are those of the physiological experiment, laboratory work in biochemistry and in bacteriology and pathology, the pharmacological experiment, all bearing more directly on modern applied medicine. It is most important, with all the detailed information and techniques that he must acquire that there be integration so that he may get a broad grasp of medicine as a whole. This means the teaching of "principles."

A principle is defined as "A truth which is evident and general, a truth comprehending many subordinate truths, a law on which others are founded or from which others are derived." For our present purpose there is an even more apposite definition—"A principle is a general truth needing interpretation and application in particular cases."

How much better the world would be today if all our conduct and all our decisions, each one, no matter how individual to ourselves or how far reaching in national or international affairs were made within the limits of a recognized "general truth" or principle.

If in the medical school we do not take the trouble to inculcate "principles" our students will fail to get that broad view of their several subjects and of medicine as a whole which is so essential to their future work. When they come to their clinical work they will be lost in a maze of unrelated facts. A large part of their time in laboratory and clinic may be wasted in going through motions with no clear idea of what these are expected to lead to.

Therefore, I am a strong believer in the formal and systematic presentation of the principles of a subject as a preliminary to or concurrent with laboratory or clinical study, being convinced that the student so

trained gains more in a shorter time from his clinical work than one who enters the clinic or the ward with no general preparation; that he is in a better position to "take notice of all the conditions in which objects or events are found," as enjoined by Sir James Paget. A neglect of "principles" results in narrowness of outlook and an inability to give each clinical and laboratory observation its due weight. Thus, the student may arrive at totally erroneous and often bizarre conclusions and diagnoses. He has been unable to apply "the principle which is a general truth to the particular case." We must try to infuse into our teaching more of the philosophic thought which has come down to us from the past and which has been forgotten or neglected in the hectic pursuit of each newly discovered fact. Such teaching can be given only by those who are imbued with the same urge to teach as the true scientist has to carry on research. Such a man should rank high in the department, for surely one of the primary functions of a medical school is to teach. It is the responsibility of teachers to ensure that their students be sent forth into the world not as mere technicians or narrow pedants but as men and women with a broad grasp of scientific and clinical principles which will guide them in any situation in which they may find themselves.

If all of this is to be done it does not seem feasible to shorten the regular medical curriculum but it might be possible to modify and curtail the length of the college course which precedes it and the intern and residency training which follows. Educators are giving thought to the possibility of devising a more concentrated and intensive college training so that it could be completed in less than four years. This would seem to be good for there are certain necessary disciplines in the way of memorizing the details of anatomy and other subjects which can be undertaken more easily by the youth of eighteen or twenty than by the young man of twenty-two or twenty-three, who has spent the preceding four years in acquiring a necessarily superficial knowledge of a number of unrelated subjects. In this we are speaking of the average student. There will always be those who can take advantage of a full college course in the liberal arts and be the better for it, no matter what profession or calling they may enter later. A necessary corollary to a shortened college course is improvement in the school curriculum which precedes it.

The five or more years given to training after graduation are necessary to equip a doctor to practice a specialty, but there might be ways

devised whereby they were not all spent interned within the confines of the hospital. This cloistered existence is not the best preparation for helping him to tackle the personality, social and community problems which will have to be faced and dealt with when he goes into practice. How such broadening experience is to be got is a matter to be worked out—perhaps by an exchange in personnel between the large teaching and city hospitals and the smaller community hospitals now existing or to be established in the future—perhaps by going back to a modification of the old apprenticeship system, whereby he is associated with members of the staff in their private practice whilst carrying on his hospital work as an extern and engaging in the study of a basic science and in research.

I hope that the pendulum has swung to its full extent in this long hospital internment and that it will come back to equilibrium as it always has after its excursions in other things pertaining to medicine.

With all the complexities of modern life, the stresses and strains of business competition, the lack of direction in family relationships and the diminishing regard for spiritual values, the physician must acquire an understanding of personality if he is to give full service to his patients and to his community. More than at any other time he must be a humanist as well as a scientist.

In his Presidential Address to this Academy four years ago that learned and loved physician, the late Dr. W. W. Herrick, put all that I have been laboring to express in one short sentence, "Without science the physician is a menace; without humanism he is no physician."

In assuming the duties and responsibilities of office I dedicate myself to the task of maintaining, with your help, all of the broad educational programmes of the Academy and of extending in every way possible its services to the public.

ADDRESS OF THE RETIRING
PRESIDENT*

GEORGE BAEHR

AFTER three eventful years as your president, I retire from office with mixed feelings of satisfaction at being relieved of its time-consuming burdens and of pleasure that this signal honor will pass to a most worthy and distinguished Fellow of the Academy. The years that I have been privileged to serve have witnessed some of the most important events in the Academy's history.

The historical significance of the Centennial Celebration in the spring of 1947 was surpassed by the general appreciation of the Fellowship that this date marked the beginning of a new era in public service. Tribute was paid to the past performances of our predecessors in a volume by Dr. Philip Van Ingen which covers the history of the Academy during its first century. In the stirring spirit of the times, the Centennial Celebration was primarily devoted to special meetings of the twelve Sections of the Academy and its affiliated scientific societies and to four three-day Institutes on Medical Education, Public Health, Hospital Development and Social Medicine, in which distinguished experts from many parts of this country and abroad also participated. The proceedings of these Institutes will appear shortly in four volumes published by the Commonwealth Fund. They can be regarded as projecting the role of the Academy during its second century in a series of Blue Prints for the Future.

The year 1947 also saw the completion of a four-year study and the publication of a report on Medicine in the Changing Order in which the Academy, with the assistance of a joint lay and medical committee, squarely faced the future prospects of impending changes in medical practice and in the methods of paying for medical care and considered the implications of these events upon medical education, scientific research and the standards of medical care in this country. In this Report, the Academy recognized the need for changes and committed itself to

* Address delivered January 6, 1949, at the Annual Meeting of The New York Academy of Medicine.

constructive proposals designed to safeguard medical education and research and to develop effective patterns of medical service under prepayment plans, which would be adaptable in a variety of ways to the special needs of the different States and their political subdivisions and to rural as well as urban areas. For their assistance in formulating our position on the looming problems of medicine in the changing order, the Academy is especially grateful to Dr. Malcolm Goodridge, Mr. Leo Wolman, Mr. John W. Davis, Dr. Iago Galdston and the late Dr. James Alexander Miller; also to the Commonwealth Fund, Milbank Memorial Fund and the Josiah Macy, Jr. Foundation for financing the study, and to the Commonwealth Fund for publishing the Report and its accompanying eleven monographs which embody its basic factual material.

The Fellowship should know that your President served as your spokesman at Senate hearings in 1947 and 1948 upon the invitation of a Senate Committee on federal medical and health legislation and with the approval of the Council of the Academy. On these occasions I reported that the Academy, after long study and serious deliberation, had taken a definite stand in opposition to National Compulsory Medical Insurance at this time, although not because of any disagreement with its basic purpose of extending medical care by means of insurance. The Academy was convinced by the studies of its special committee that this objective could be attained in a much more efficient and decidedly less hazardous manner by means of federal assistance to the States and local areas in the form of grants-in-aid for the dual purposes 1) of developing adequate state and local programs of medical care meeting high standards and 2) of establishing prepayment plans which would support these programs. The Academy favors voluntary efforts at this time because of their greater flexibility and the opportunity they can provide for experimentation with newer methods of medical service under prepayment. It is convinced that the rapid extension of such programs to all the people awaits the enactment of the supporting federal and state legislation which it has in mind.

At this moment when such legislation is in preparation, the Academy considers it important to re-emphasize the pitfalls in an exclusively fee-for-service method of remunerating the participating physicians under any plan, voluntary or compulsory. Although there is no immediate substitute for this method of remunerating physicians, it is vitally im-

portant for the ultimate success of any prepayment plan that it encourage and support medical group practice, for it can advantageously accept payment on a per capita basis which is actuarially measurable and can serve as the yardstick for measuring the adequacy of medical care under a prepayment program, both qualitatively and quantitatively. It is also important to stress the necessity for comprehensive medical care (in contradistinction to limited coverage for catastrophic illnesses) as essential for the development of preventive medical services. It should be self-evident that government ought not to spend tax funds nor the people make their contributions for medical care exclusively for the diagnosis and treatment of the end results of disease, when preventive medicine is also purchasable.

I cannot refrain from restating these three elementary observations concerning payment for medical services, group practice and comprehensive medical care, for they have been ignored in recent federal bills for national compulsory medical insurance, as well as in most of the Blue Shield plans supported by organized medicine. Because of these deficiencies the Academy, while advocating voluntary medical insurance, recognizes the deficiencies of the present Blue Shield plans because of their limited scope as it does the extreme federal proposals for immediate universal coverage. Being motivated solely by the public's interest, it believes that the truth lies in between.

It is indeed regrettable that an opportunity was recently lost to put a national voluntary program of medical insurance into operation under a program sponsored jointly by the National Blue Cross and Blue Shield Associations. The proposed joint insurance plan had many defects but to my mind it had at least the merit of getting a national voluntary program established under responsible public, medical and hospital auspices which could be modified and expanded as required by local variations in medical and hospital benefits. Unilateral action by Blue Cross or Blue Shield is doomed to failure for it cannot stem the tide. If joint action by both associations is eventually consummated, the many community-sponsored, industry-sponsored and cooperative medical care plans which are in successful operation in all parts of the country cannot be ignored. Many have the support of the rapidly growing health and welfare funds of large industries and labor unions and unless they are taken into the fold and their beneficiaries provided with comprehensive medical care of satisfactory scope and quality by a national

voluntary agency or agencies, the pressure for federal compulsory medical insurance will continue unabated until such legislation is enacted.

In accordance with its tradition, the Academy should continue to abstain from activities concerned with so-called medical economics which are the responsibilities of State and county medical societies and of the American Medical Association. It cannot refrain, however, from devoting its most earnest consideration to the implications for medical practice and for medical education and research inherent in prepayment methods and changing patterns of medical service. In these fields, the Academy should be prepared to assist in giving direction to the tide which is sweeping us onward so that it may not engulf and destroy the medical institutions and services of the country in which we take justifiable pride. Upon the advice of the Council, a new Committee on Medicine in the Changing Order has recently been appointed which will study evolving patterns of medical care under prepayment plans and their effects upon preventive as well as curative medicine and upon education and research.

One of the most important events in the recent history of the Academy was the establishment within the past year of a twelfth Section devoted to Microbiology. Ten of the existing Sections are concerned with the various special branches of medicine and surgery and the eleventh with Historical and Cultural Medicine. The new Section on Microbiology has already attracted large numbers of workers in the fields of bacteriology, immunology, virology, parasitology and chemotherapy into the fellowship of the Academy and has therefore materially extended the scope of the Academy's activities into basic scientific research. Under the chairmanship of Dr. Gregory Schwartzman, and with the support of Drs. Frank Horsfall, Jr., Colin MacLeod, Rene Dubos, John G. Kidd, Ralph Muckenfuss and Harry Most, the Section has had many rewarding programs of original work during the past year, which have attracted the attention of scientists throughout the country. Abstracts of these proceedings are now printed regularly in the Bulletin of the Academy and the important papers read at three two-day symposia conducted by the Section during the last twelve months, will shortly be published by the Columbia University Press in a series of three volumes. I look forward with anticipation to the establishment of a similar scientific Section devoted to physiology, biochemistry and biophysics in the near future.

The completion of the Academy's first century required a re-evaluation of our physical, financial and professional abilities to carry our responsibilities forward into the future. The demands of the public upon our medical library, one of the largest in the world, and upon the Academy's services in medical education, public health and medical information have grown with the years. Since World War II salaries and other operating costs have increased about 78 per cent, whereas income from endowments has fallen in relation to the purchasing value of the dollar. The dues of the Fellows have been increased, yet the income from this source covers only one fourth of the Academy's normal budget. The remaining three fourths must be met each year out of interest from endowments, bequests, contributions and other sources. To avoid the deficits of recent years which were met out of a small and diminishing reserve, the Trustees took drastic measures in adopting last year's budget. Not only dues, but every other possible source of income was increased, the budgets for Medical Education, Public Health Relations and Medical Information were each slashed 20 per cent and the library was held to economies which would not affect its efficiency too seriously. In addition, the library was regrettably closed on Saturdays. These measures enabled us to end the year 1948 without a deficit. However, pride in this accomplishment is tinged by the knowledge that this was made possible largely because of the windfall of exceptionally large year-end dividends on equities, a good fortune which may not recur in 1949.

For the year 1949, the Trustees have been obliged to adopt a budget with an anticipated deficit of \$45,000, in spite of the continuance of previous economies including the 20 per cent cut in the budgets of the three Standing Committees. This situation is due to a cost-of-living wage increase of 10 per cent for employees and to other unavoidable increases in the operating expenses of the Library, such as the reopening of the Library on Saturdays, for which there has long been a well-justified clamor.

Although the basic financial structure of the Academy was never more secure than at the present moment, there are no funds in sight for the normal growth of the library without sacrificing all the Academy's other important public responsibilities. The dilemma has only one solution, more vigorous efforts by all fellows and lay friends of the Academy to increase its endowment by bequests and gifts of a mil-

lion dollars. This should not be too difficult of accomplishment for the Academy never held a higher place in public esteem than at this moment.

The library presents another problem which urgently requires solution. As I mentioned last year, its book stacks are filled to maximum capacity and a substantial addition to the stack building must be made promptly. A building fund of \$325,000, most of which was raised in recent years by Dr. Harold Mixsell's Steering Committee, now proves to be about half the amount required for this purpose. To my mind, this is the most urgent problem which my successor, Dr. Watson, will inherit. Its solution will not brook delay without adversely affecting the efficiency of library services in a most serious manner. It is possible that we shall shortly be able to announce a building program which will correct the existing deficiencies for many years to come, but it will require the combined efforts of the entire Fellowship for accomplishment.

The burdens of a president are lightened by the other officers of the Academy and the many devoted members of its staff, who labor faithfully throughout the years without sharing equally in his glory. I cannot mention them all, yet I cannot leave this office without commenting upon our good fortune in having Dr. Howard Craig as director. With extraordinary tact and wisdom, his day by day guidance of the many complex activities of the institution assures it a continuity of purpose despite changing officers and personnel. The Trustees have watched faithfully over the Academy's finances during these years, but the Fellowship owes a special debt of gratitude to the chairman of the Board, Dr. Orrin S. Wightman and to the Chairman of its Executive Committee, Dr. Shepard Krech for the constancy of their vigilance. In spite of the best banking advice in the City, we would not be in a strong position today if it were not for the time and thought which they gave daily to safeguarding our financial structure, aided by our competent comptroller, Mr. Arthur Eberle.

The loss of Dr. James Alexander Miller, past President of the Academy, as Chairman of the Committee on Public Health Relations leaves a void which cannot be filled. Rarely does a generation produce a physician and public benefactor with comparable attributes as a leader in public health and medicine. The work of this Committee is fortunately safeguarded by the fact that it can continue to lean on its able and distinguished Executive Secretary, Dr. E. H. L. Corwin who, like

Dr. Miller, has continuously served and guided the Committee since its establishment thirty-eight years ago.

The Committee on Medical Education has greatly broadened the scope of its activities under the chairmanship of Dr. Paul Reznikoff and with the devoted assistance of its Executive Secretary, Dr. Mahlon Ashford. In the work of this Committee I must single out for special mention Dr. Carl Eggers, Dr. Condict Cutler, Dr. Louis J. Soffer, Dr. Ross Golden, Dr. Frank Hanger and Dr. Alfred Angrist, who have been chiefly responsible for the success of the Graduate Fortnights, especially the last one on Recent Advances in Therapy. The next Graduate Fortnight will be on Recent Advances in Diagnostic Techniques.

As in previous years, the Committee on Medical Information has been guided by its chairman, Dr. Harold Mixsell with the assistance of Dr. Donald Armstrong as chairman of its Executive Committee and Dr. Iago Galdston as its able Executive Secretary. To them, to the 250 fellows who serve on the various Standing and Special Committees and to the staff of the Academy who do its daily work with loyalty and unflagging zeal, the entire Fellowship should be profoundly grateful.

NEW ANALGESIC DRUGS *

HENRY B. VAN DYKE

Hosack Professor of Pharmacology, College of Physicians and Surgeons
Columbia University

A DECADE ago, morphine and alkaloids closely related to it were still the most powerful drugs the physician could use to relieve pain. With the discovery of the analgesic action of meperidine as reported by Eisleb and Schau-mann in 1939,¹ a new potent synthetic drug became available. During the war German chemists and pharmacologists apparently continued to work actively and discovered other synthetic substitutes for morphine. Among the best known of these is methadone which has been extensively studied following reports by American² and British teams sent to investigate the work of the pharmaceutical division of the I. G. Farbenindustrie at Höchst am Main. A third new analgesic drug, metopon, is methyl dihydromorphinone and like dihydromorphinone is related to morphine. It was prepared in this country by Small in 1936. The three drugs, metopon, meperidine and methadone will be discussed as new drugs useful as substitutes for morphine.

Evaluation of analgesic drugs. I. Analgesia. Analgesic drugs act on the cerebrum to relieve pain without seriously affecting consciousness. Modern experimental methods for their investigation employ both animals and human subjects after the organic chemist has made a new compound. All preliminary experiments, including toxicological studies, must be performed in animals in which only the *reaction* to pain can be observed. In man, the perception of pain can also be studied. Early methods were so crude that little more than the presence or absence of analgesia could be determined. Dozens of methods have since been employed and most of them have little value for comparative quantitative purposes. Painful electrical stimulation of the skin or mechanical methods such as applying graduated pressure to the rat's tail are unsatisfactory quantitatively. Heat, usually as thermal radiation, is today a favorite painful stimulus for comparing analgesic drugs in animals and

* Given October 13, 1948 at the 21st Graduate Fortnight of The New York Academy of Medicine.

man. The pioneer work of Hardy, Wolff and Goodell,³ who used radiant heat to stimulate pain-receptors in the skin of human subjects, stimulated much interest in thermal-radiation methods which have been adapted with considerable success to rats, guinea pigs and dogs. Only a few examples^{4, 5, 6} among numerous references need be cited. Other algesimetric methods applied to man or animals or both have endeavored to employ deeper or different receptors as by electrical stimulation of the tooth pulp,⁷ esophageal distention,⁸ or muscle ischemia in association with repeated muscular contractions⁸ (method of Alam and Smirk).

There are many factors which modify either the perception of pain or the reaction to it. Likewise the analgesic response to drugs can be greatly altered by the intensity of pain, anxiety, mood, fatigue, suggestion, etc. Limits of space prevent a complete discussion of the conditions under which the perception of pain and the response to analgesic drugs are unusual.

II. Addiction and tolerance. Potential addiction with all that this term connotes has to be considered when any drug used to relieve pain undergoes therapeutic evaluation. Drugs which resemble morphine in their clinical analgesic effects, although their chemical relationship, if any, is obscure, can be shown by careful observations and by appropriate experiments to exhibit some features of the addiction-withdrawal syndrome characteristic of morphine. Certain terms must be agreed upon in discussions in this field. Habituation is the production of psychic dependence on a drug and need not be accompanied by tolerance or objective withdrawal symptoms. Addiction is the development of psychic and physical dependence on a drug and probably is associated with tolerance which is particularly great in morphine addicts. Physical dependence in the addicted primate is demonstrated and measured by the syndrome appearing after withdrawal of the drug. (Evidence for psychic dependence usually can only be secured in man.)

The study of addiction is a troublesome and complex subject in which quantitative data necessary for comparisons of drugs are difficult to secure. Good studies can probably be made only in the monkey, higher primates and man. An account of morphine addiction and the withdrawal syndrome in the rhesus monkey is given by Seevers⁹ who compared dihydromorphinone (Dilaudid) with other alkaloids derived from opium.¹⁰ Interesting data have been secured from human studies particularly those of workers in the United States Public Health Service

TABLE I—DAILY SCORE OF POINTS FOR ABSTINENCE SYMPTOMS
(Kolb and Himmelsbach,¹¹ 1938)

Quantitative

1 point each:

Specified rises in rectal temperature, respiratory rate and systolic blood-pressure. Loss of 1 lb. of weight.

Non-quantitative

1 point each:

Yawning, lacrimation, rhinorrhea and perspiration.

3 points each:

Anorexia, goose-flesh, mydriasis and tremor.

5 points each:

Restlessness and vomiting.

which maintains a hospital in Lexington, Kentucky. Himmelsbach, Isbell, Wikler and their coworkers are especially associated with the investigative work of this hospital. The best effort to evaluate quantitatively the human abstinence syndrome—the measurement of physical dependence—was reported by Kolb and Himmelsbach¹¹ in 1938. A summary of their assignment of points is given in Table I. Numerous morphine addicts have been studied with reference to the course of the abstinence syndrome after the withdrawal of the drug. Charts of the intensity of symptoms (given as points) plotted against time permit comparisons of new drugs with morphine. Crossed tolerance to morphine (substitution for morphine in addicts) and the intensity and duration of abstinence symptoms. (physical dependence) in comparison with morphine can thus be studied in man. Examples will be discussed with reference to substitutes for morphine. It is important to emphasize that most addicts to the morphine group of alkaloids belong to a special “constitutionally inferior” group. Too sweeping generalizations concerning the likelihood of addiction to a new drug administered to normal persons must be guarded against if such generalizations are based only on experiments in addicts.

METOPON

Metopon is closely related to dihydromorphinone (Dilaudid) from which it differs in possessing a methyl group attached to the phenanthrene ring. The latest report on this drug was prepared by N. B. Eddy.¹² It is recommended as a substitute for morphine for the relief

of chronic pain and its use until recently has been restricted to patients with malignant neoplasms.

Animal experiments¹³ revealed that metopon is a much more potent analgesic drug than morphine but that it is likewise much more toxic. However, in terms of its analgesic potency metopon is believed less likely to cause sedation, emesis or excitation. Himmelsbach¹⁴ studied the effects of the drug in morphine addicts in whom it was substituted for morphine in doses which, although one-seventh as great, were administered twice as often. During the period of substitution, the addicts derived less satisfaction from metopon than from morphine. When metopon was withdrawn, the abstinence syndrome appeared more abruptly but was less severe. These data suggested that addiction to metopon might be less pronounced than that to morphine.

The recommendation that metopon be used as a morphine substitute when a potent analgesic is required by sufferers from cancer was based upon laboratory and clinical observations reporting that it has several advantages over morphine.¹² Clinically it is about twice as potent and is relatively highly active when administered orally. Analgesic doses cause little respiratory depression and less sedation with associated mental lethargy. Emesis is rarely observed after its use. Euphoria is considered to be less than after morphine. In the patient who has received no morphine or related analgesic previously, tolerance appears to develop slowly. For example, the same daily dose was administered to 164 patients for 1-20 weeks; however, many of these patients obtained less relief from pain the longer medication was continued. The more recent report of Houde, Rasmussen and La Due¹⁵ is not favorable. They studied carefully 5 cancer patients receiving frequent oral doses as high as 18 mgm. each. Only one patient who had not received morphine or Pantopon was relieved of pain.

Toxic or unpleasant effects in cancer patients were found to be infrequent in Eddy's clinical evaluation.¹² In 1502 patients none was reported. Nausea was the most frequently mentioned toxic effect (87 cases) yet only 10 per cent (27 cases) of 277 patients experiencing nausea in association with previous medication complained of this symptom when metopon was used as an analgesic. Less frequent complaints were restlessness, headache, perspiration, dryness or burning "in the throat or stomach," dizziness, etc.

Metopon is marketed only for oral use as capsules each containing 3

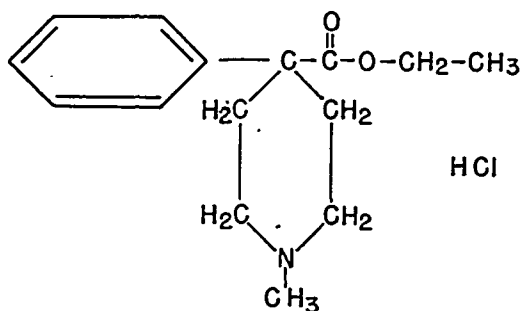
mgm. The dose in the non-tolerant person who has had no analgesic of the morphine group is 6 mgm. for an adult. The "chronic pain" for which its use is best justified is that associated with malignant neoplasms or their metastases from which recovery is improbable. Even in such patients, administration should be as infrequent and irregular as possible with periods of complete withdrawal so as to postpone addiction and tolerance as long as possible. Any other use requires the same precautions the physician must employ with morphine. In the majority of cancer patients, to whom the administration of metopon has heretofore been restricted, two to three doses per day have usually been employed; some physicians have observed an analgesic effect for five to ten hours but in a few cases, analgesia lasted only an hour or even less.

Summary. Metopon may be classified as an effective analgesic of the morphine group. It is active by mouth and appears to cause nausea, vomiting, and sedation with mental dullness less frequently than morphine. Whether it is really superior to dihydromorphinone (Dilaudid) in these respects has not been proved. Metopon is probably not a satisfactory analgesic in patients who have already received repeated doses of morphine. As with morphine, addiction and the development of tolerance with physical and psychic dependence can follow its repeated administration although these phenomena are believed to be less severe than after morphine. The dangers of addiction are much greater than with the purely synthetic analgesics, meperidine and methadone, which are much to be preferred if either can be used satisfactorily.

MEPERIDINE

Meperidine (syn. Demerol, Dolantin, isonipecaine, pethidine) was the first synthetic drug to be marketed as a potent analgesic. Eisleb and Schaumann¹ were studying synthetic spasmolytic agents of a related nature and discovered that meperidine not only relieved spasm of isolated smooth muscle but also prevented reactions to painful stimuli in mice. Clinical reports^{16,17} confirming their findings appeared the same year (1939). Today the drug is extensively used and can be regarded as more potent than codeine and often nearly as potent as morphine. It is perhaps without a rival as an obstetrical analgesic. Its structural formula is shown in Fig. 1.

The pharmacology of meperidine. The first studies of the pharmacology of meperidine were made by Schaumann^{1,18} who emphasized



MEPERIDINE (DEMEROL)

Figure 1

two outstanding effects of the drug: (1) analgesia with little associated sedation from an action on the central nervous system and (2) a spasmolytic action on smooth muscle whether contraction was caused by a cholinergic drug or nerve stimulation or by a musculotropic agent like histamine or barium ions. Other general studies were made by Duguid and Heathcote¹⁹ and Gruber, Hart and Gruber.²⁰

A number of investigators, using the more exact algometric methods available today for both animals and man, have confirmed the first German reports. Particularly favored are painful thermal-radiation stimuli similar to those used by Hardy, Wolff and Goodell; the reports of Ercoli and Lewis⁴ using rats and of Christensen and Gross²¹ using human subjects furnish examples of comparisons of meperidine with morphine and other analgesic drugs. The clinical use of meperidine as an analgesic will be discussed later.

The other effects of meperidine on the central nervous system are chiefly of toxicological interest. It has little sedative or depressant action. On the contrary, large doses provoke a diffuse excitation manifested by tremors, jerking movements and finally convulsions. A recent description of the symptoms in mice and rabbits will be found in Way's article.²² The effects of large doses on the human cerebrum were particularly studied by Andrews²³ who administered as much as 3.18 grams of meperidine in 24 hours to men formerly addicted to morphine. Nervousness, disorientation, tremors and jerking movements of the extremities appeared. Abnormally slow waves in electro-encephalograms were associated with these clinical signs. The electro-encephalographic

changes together with sudden losses of consciousness, uncontrolled abnormal movements and tongue-biting suggested that poisoning by meperidine can provoke epileptiform changes in cerebral activity.

Pharmacological experiments readily demonstrated that meperidine depresses respiration apparently by a central action. Such an effect has rarely been observed after clinical use except in patients with intracranial lesions.²⁴ Way²² showed that convulsions preceding death can mask the respiratory depression following large doses of meperidine. If the convulsions are controlled by a barbiturate, paralysis of respiration appears. Miosis is not seen after meperidine except in some patients with intracranial disease.²⁴ On the other hand, the drug can cause corneal anesthesia by a central action. (It is also a local anesthetic but, like methadone, is too irritating to be of clinical value.^{25, 26})

The first experiments with meperidine demonstrated that relaxation of smooth muscle when in spasm can be readily evoked especially with isolated intestine. Some of this effect can be attributed to an atropine-like action for which there is other evidence (antagonism of salivary secretion after pilocarpine or of bradycardia after acetylcholine^{1, 19}); however, the parasympatholytic action is trivial in comparison with atropine. Spasm owing to a musculotropic agent such as histamine acting on the intestine or bronchi is relieved *in vitro*. Similarly, antagonism of histamine spasm of the intestine can be observed in acute experiments in intact animals.¹⁹ Other experiments in intact animals or in men yielded opposite results. Careful experiments in normal men and dogs showed that meperidine usually evokes contraction of the small intestine,^{20, 27, 28, 29} although Batterman's experiments in man (stomach, ileum, colon) led him to conclude that the effect of meperidine is purely antispasmodic.³⁰ The contradictory findings have been partly reconciled by postulating that only when the intestine is in abnormal spasm is it possible to demonstrate the relaxing effect of meperidine. Karr³¹ found that the propulsive activity of the gastrointestinal tract of rats is reduced after meperidine but not to nearly as great an extent as after morphine and less than after methadone. In patients, meperidine does not have a constipating effect.

Like codeine and morphine meperidine causes spasm of the sphincter of the common bile duct (sphincter "mechanism" of Oddi) so that the intrabiliary pressure rises and is sometimes associated with colic. This conclusion was reached from studies of changes in intrabiliary

pressure in patients with drainage tubes in the common bile duct.³² The response of the uterus is variable and often in a direction opposite that of its initial state.^{20, 27} What information is available concerning the response of the human pregnant uterus indicates that the action of meperidine, if any, is to promote contractions. Climenko and Berg³³ observed little effect on the intact human ureter following the administration of therapeutic doses of meperidine unless ureteral tone was high. The drug then had a spasmolytic effect and inhibited ureteral contractions.

Cardiovascular effects of ordinary doses of meperidine are of little importance. Changes such as bradycardia and hypotension are greater after large doses or after small doses intravenously. The hypotensive action, which is also observed after morphine or methadone is caused by a direct action on the vascular musculature. Shideman and Johnson³⁴ investigated tolerance and crossed tolerance of the hypotensive action of meperidine, morphine and methadone. Tolerance to meperidine was only partial and there was no striking crossed tolerance to either morphine or methadone.

Some information concerning the fate of meperidine has been gathered. Usually it cannot be detected in the blood after intramuscular injections of 100 mgm. into man (Way and others³⁵). In rats, the highest tissue concentrations were found in the lungs, liver, kidney and spleen. Meperidine is probably destroyed by an esterase found only in the liver. The enzyme is different from that hydrolyzing esters of tropines, choline or aliphatic substances.³⁶ Hepatic disease conceivably could interfere with its destruction³⁷ About 10 per cent of a dose escapes destruction and is excreted in the urine regardless of the dose or the presence of tolerance.^{38, 39}

Other phenylpiperidines related to meperidine have been studied and preliminary reports^{2, 40-45} suggest that some will be of great interest both experimentally and clinically. For example, Schaumann¹ stated that Bemidon or No. 10446 in the German series, which differs from meperidine only by the addition of an hydroxyl group in the 3-position of the phenyl ring, can be used for severe operations not requiring muscular relaxation. There is said to be no serious interference with consciousness or voluntary movement but respiration is not adequate unless the patient is repeatedly instructed to breathe.

The clinical use of meperidine. The early German reports of the

excellent clinical analgesia following the administration of meperidine have been largely confirmed and much extended by careful work in other countries. Meperidine can be given orally but is a more reliable analgesic after intramuscular injection. By either route the preferred dose is 100 mgm. repeated every 4-5 hours if required. Its potency in therapeutic doses is greater than that of codeine. Its toxic effects, if present, are usually not serious. Its antispasmodic effects probably are not important and are difficult to judge because the only valid use of meperidine is for analgesia which may modify signs or symptoms of smooth muscle spasm.

Batterman and his coworkers published several reports justifying the use of meperidine as a substitute for morphine.^{30, 46, 47, 48} Another recent general paper is that of Noth, Hecht and Yonkman.⁴⁹ The analgesic potency of 100 mgm. of meperidine parenterally approaches that of 10 mgm. of morphine administered subcutaneously. Almost all types of pain are relieved by meperidine. For example, in 849 hospital patients in whom the drug was substituted for morphine and administered parenterally, relief of pain was complete in 85 per cent and moderate in an additional 11 per cent.³⁰ Very severe pain was completely relieved in 60 per cent of the patients of Noth and others⁴⁹ and there was partial relief in an additional 18 per cent. Sedative effects were slight in comparison with morphine, but apparent sedation could be observed when pain was relieved.⁴⁹ Meperidine does not cause constipation. It does not lessen cough. Its only special effect on the eye is partial anesthesia of the cornea; miosis is not ordinarily present and there is no effect on accommodation.

Certain special uses of meperidine deserve mention. On the basis of their use of the drug for pre-anesthetic medication as a substitute for morphine in 338 patients, Rovenstine and Batterman⁵⁰ considered that meperidine is as satisfactory as morphine ("psychic sedation," ease of induction, reduced need for general anesthetic) and in some respects is superior (less respiratory depression, less nausea and dizziness, less secretion of mucus and saliva). (Robbins found that the cardiac irregularities always appearing in dogs anesthetized with cyclopropane after premedication with morphine, were never observed after parenteral premedication with meperidine.⁵¹) Post-anesthetic medication with meperidine was highly recommended by Batterman and Mulholland⁴⁷ who emphasized its lack of depression of respiration or the cough reflex.

Meperidine appears to be the safest potent analgesic for obstetrical use, endangering neither the mother nor the child and not retarding labor.⁵²⁻⁵⁷ Scopolamine or barbiturate in reduced dosage is often combined with meperidine to induce amnesia. Meperidine has been used in various doses. A common practice has been to inject 100 mgm. intramuscularly and to repeat this dose once or twice if needed, at intervals of 1-2 hours. Intramuscular injection is preferred. Toxic effects such as dizziness, flushing, dryness of the mouth, and nausea are not serious and appear to be less frequent than for other clinical uses of meperidine.

Guttman²⁴ reported that peculiar toxic effects were observed in a high proportion (35 per cent) of 20 patients with intracranial lesions. The most serious sign was a depression of respiration manifested by a respiratory rate of 12 or less per minute. Associated changes were bradycardia, miosis with a sluggish pupillary response and, frequently, a corneal anesthesia. Meperidine is not a suitable analgesic for such patients. According to Gaensler, McGowan and Henderson³² it may be dangerous to use meperidine as an analgesic after cholecystectomy since a biliary fistula might be caused. The drug was found to cause spasm of the "sphincter" of Oddi leading to increased intrabiliary pressure similar to the change after morphine, which produces an even greater increase in intrabiliary pressure. Meperidine could precipitate an attack of biliary colic. It did not cause contraction of the gall bladder.

The toxic effects of therapeutic doses of meperidine may be annoying and sometimes are frequent, especially in ambulatory patients.^{30, 46-49} They rarely are serious and only infrequently require discontinuance of the drug. Batterman³⁰ observed one or more toxic effects in 63 per cent of ambulatory patients taking the drug orally but in only 26 per cent of hospitalized patients receiving parenteral injections. Noth, Hecht and Yonkman⁴⁹ reported the same incidence (27 per cent) of toxic symptoms in their hospitalized patients. Dizziness (sometimes described as lightheadedness) is the commonest symptom. Nausea or vomiting or both probably occur less frequently than after morphine. Flushing, perspiration or dryness of the mouth are frequent complaints. Syncope may occur in ambulatory patients. Euphoria which presumably would facilitate habituation was noted in early German reports,^{58, 59} especially in potential addicts. A euphoric response to meperidine was observed in 5-8 per cent of American patients.^{30, 49} Delirium is an exceptional toxic effect⁵⁸ except after doses greatly exceeding those of

therapeutic value. A similar statement holds for the myoclonic contractions observed by Kucher⁵⁹ in two meperidine addicts. The effects of very large experimental doses which can cause "cerebral irritation" with nervousness, disorientation, delirium, tremors, and coarse jerking movements in man have been described by Andrews²³ and by Himmelsbach.^{46, 60}

Addiction and the development of tolerance to meperidine. The addiction liability of meperidine in morphine addicts or in persons who are potential addicts was recognized in Germany within a year after the introduction of meperidine.^{58, 59} Although primary habituation or addiction to meperidine can occur, as illustrated by the two recent reports of Wieder⁶¹ and of Curry,⁶² the drug is agreed to have a low addiction liability in normal patients. In those addicted to morphine or related drugs, meperidine may be used as a less-desired substitute for morphine. Meperidine can cause severe primary habituation or addiction in the abnormal individuals who are potential addicts. For these reasons its distribution has to be regulated.

Careful attempts have been made by Himmelsbach and Andrews^{46, 60, 63, 64} to define in rough quantitative terms the addiction liability of meperidine. The experimental subjects were either morphine addicts or former addicts. In the addict in whom meperidine was substituted for morphine, the abstinence syndrome to be expected if no substitute had been given was only partially relieved by meperidine. Meperidine was not recommended for treating the severest types of abstinence symptoms after morphine withdrawal since dangerous doses of meperidine would have been required. (Methadone is the preferred drug for this purpose). Physical dependence on meperidine (demonstrated by objective withdrawal signs) was definite but mild in comparison with morphine. The abstinence syndrome was less intense and its duration was shorter. The addiction liability of meperidine was probably less than that of codeine. Tolerance of the toxic effects of meperidine was slight and it was difficult to exceed doses of the order of 3 grams in 24 hours (about three to five times a heavy therapeutic dose) which was seriously toxic in subjects with experimental addiction. Tolerance of the analgesic action of meperidine was much slower in appearing than after morphine. Andrews' algometric tests by the method of Hardy, Wolff and Goodell revealed that maximum tolerance was not reached until increasing doses had been taken for about 8 weeks.⁶³ A

remarkable finding was the persistence of tolerance to analgesia after 100 mgm. of meperidine for at least 30 days after the drug was withdrawn.

Summary. Meperidine (Demerol) is a potent analgesic drug which can often be used as a substitute for morphine. It is active orally but more dependable after intramuscular injection. The dose by either route is 100 mgm. Its antispasmodic effects are usually not important; on the other hand its spasmogenic action may be significant as in disease of the biliary tract. The atropine-like effect of meperidine is quantitatively trivial.

It differs from morphine in causing less respiratory depression, less sedation, less euphoria, no suppression of coughing, no interference with gastro-intestinal motility and less dizziness or nausea. It is the best available analgesic drug for use in obstetrics. It has been highly recommended for pre-anesthetic medication and appears to be superior to morphine for post-operative use. It can be used successfully as a substitute for morphine for the relief of many types of pain.

Toxic effects accompanying therapeutic use which are especially frequent in ambulatory patients, have not been shown to be more frequent than if morphine had been similarly employed. These effects are rarely serious and include dizziness, flushing, perspiration, dryness of the mouth, euphoria, nausea and vomiting. In normal persons receiving meperidine for reasonable periods, there is not great likelihood of habituation or addiction. However, primary addiction can be induced but is less serious than after morphine. Tolerance of analgesic doses after repeated use develops slowly. Tolerance of toxic effects is never comparable to that of morphine.

METHADONE

Methadone (syn. amidon, Dolophine, Adanon, miadone, 10820) is a comparatively simple synthetic drug with an analgesic potency equal to or exceeding that of morphine. Its structural formula is shown in Fig. 2. It is believed to be among the best of a series which German chemists and pharmacologists discovered during the war. The first American report of this was made by Kleiderer and his colleagues.² Strangely enough, despite a shortage of morphine, the drug was discredited in Germany probably because excessive doses were used.⁶⁵

The pharmacology of methadone. Pharmacological studies of metha-

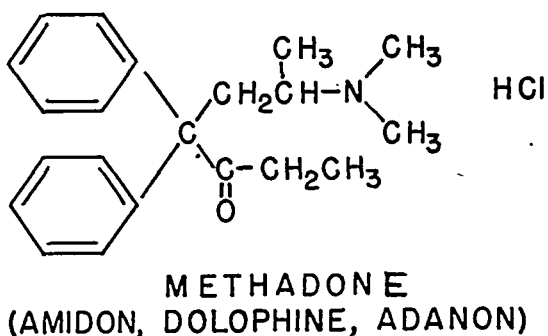


Figure 2

done have been made particularly by Chen, Scott and their co-workers.^{28, 65, 66, 67} The important effects of the drug are on the central nervous system. In experimental studies in the rat, dog and man, the analgesic action of methadone is about twice that of morphine if salts of each drug are compared on a weight basis. The most accurate experiments were performed by using thermal radiation as the painful stimulus by the method of Hardy, Wolff, and Goodell. Other data on the analgesic action of the drug will be considered later when its clinical use will be discussed.

There is little sedation with analgesic doses but this effect can be recognized with larger doses. Likewise larger doses appear to depress the respiratory center so that the respiratory rate falls. Lethal doses in animals paralyze the respiratory center. Like morphine and meperidine, methadone has mixed depressant and stimulating effects on the central nervous system. In animals it stimulates the vagal centers thus causing bradycardia and increased intestinal movements. It is probable that its emetic action, peculiar to man, is to be attributed to central stimulation of the vomiting mechanism. Its effects on the spinal cord resemble those of morphine and like the latter it evokes a characteristic erection of the mouse's tail (Straub phenomenon) probably by an action on the cord.

Considerable attention has been given to the effects of methadone on smooth muscle. In the intact animal, the movements of the small intestine are increased owing to central vagal stimulation. The propulsive activity of the intestine may be reduced but not nearly as greatly as after morphine.³¹ The isolated intestine relaxes if methadone is added

to the fluid bathing it. This effect appears whether initial contraction of the isolated intestine is caused by a musculotropic agent such as histamine or by a cholinergic drug such as acetylcholine and probably represents a direct action of methadone on the smooth muscle of the gut. The effects on the uterus are variable but usually are represented by a reversal of the initial state of relaxation or contraction.^{65, 68} Relaxation of the ureter *in situ* has been reported after the injection of methadone into anesthetized dogs.⁶⁵

Small intravenous doses of potent analgesic drugs, such as morphine, meperidine or methadone, cause an acute fall in blood pressure. Schmidt and Livingston were the first carefully to study this phenomenon after the injection of morphine and reported that an acute tolerance appears so that successive doses of morphine cause a diminishing effect. Shide-man and Johnson³⁴ investigated the development of this "acute tolerance" in dogs, receiving morphine, meperidine or methadone. Tolerance to the long depressor effect of methadone conferred no crossed tolerance to morphine or meperidine and tolerance to the hypotensive effect of morphine did not affect the hypotensive action of methadone.

Nothing is known of the fate of methadone beyond the fact that a fraction of the dose (e.g. 13 per cent or less) appears in the urine.⁶⁹

The single acute lethal dose of methadone is much lower than that of morphine so that compared on a weight basis methadone is from seven (guinea pig) to eighteen times (rat) as toxic as morphine.⁶⁵ Death is caused by respiratory paralysis. The acute lethal dose of an intravenous injection of morphine is much lower in very young or in aged rats whereas the similar dose of methadone is little changed in various age groups.⁷⁰ Chronic poisoning which will be discussed in connection with addiction does not lead in animals to recognizable morphological changes in various organs.

Pharmacological studies and initial clinical trials of isomers and derivatives of methadone deserve brief mention since they suggest that other good synthetic analgesics will soon be available for clinical use. Methadone itself is marketed as a racemic mixture. There is unequivocal evidence that the levo-isomer is the active portion of the mixture.^{67, 71, 72} Scott, Robbins and Chen⁶⁷ showed that levo-methadone is about fifty times as active as dextro-methadone when tested in man by the thermal-radiation method of Hardy, Wolff and Goodell. Tests of the addicting properties of the two isomers by Isbell and Eisenman⁷² likewise dem-

onstrated that only the levo-isomer is active. Those interested in compounds related to methadone either as isomers or derivatives are referred to the publications just mentioned as well as those of other investigators.^{2, 41, 65, 73}

The clinical use of methadone. The analgesic potency of methadone in comparison with morphine varies with the observer and the conditions under which he makes comparisons. Careful experiments with the apparatus of Hardy, Wolff and Goodell have shown methadone to be two to three times as potent as morphine.^{69, 74, 75} Another clinical comparison found less difference in the analgesic dose of the two drugs.⁷⁶ It is fair to conclude that weight for weight, methadone is at least as potent as morphine and that many clinical demands for a powerful analgesic drug have been met by considerably smaller doses than would be customary for morphine. The drug is often satisfactory by mouth although analgesic action is slower (30 minutes or more) and a larger dose is sometimes necessary. For non-productive cough small oral doses (1-2 mgm.) are sufficient. Troxil⁷⁷ states that subcutaneous doses act in 15 minutes and that severe pain can be controlled by 7.5-10.0 mgm. of methadone. (The severity of pain determines whether larger or smaller doses should be used.) The duration of analgesic action is usually 3-4 hours but may extend to 8-10 hours or persist only for two hours depending upon the type of pain.

Numerous clinical observations indicate that methadone is as good an analgesic drug as morphine. Special clinical needs are sometimes met better by morphine, sometimes by methadone. For example, sedation and euphoria are slight with methadone which is therefore considered inferior to morphine as a pre-anesthetic drug.^{21, 78} On the other hand, in severe pain associated with spasm of the urinary bladder methadone is effective whereas morphine is rarely useful; also methadone is a satisfactory analgesic in ureterolithiasis.⁷⁸ (In intact animals morphine causes ureteral contraction and methadone relaxes the ureter.) Methadone has been used as a substitute for morphine in routine medical and surgical cases as well as for patients with special disorders such as occlusive vascular disease or neurological disturbances.^{21, 76, 78-82} Satisfactory to excellent relief was obtained in 80 per cent or more patients receiving a dose of about 10 mgm. (Batterman and Oshlag⁸³ considered methadone to be an unsatisfactory analgesic; however, their experience appears to be exceptional.) In advanced cancer, a severe test for any

analgesic, methadone gave satisfactory relief in 66 per cent of 50 cases.¹⁵ Methadone is not suitable for analgesia in labor.^{77, 84, 85} Analgesia may be unsatisfactory. Depression of fetal respiration occurs with sufficient frequency to contraindicate the use of the drug as an obstetrical analgesic. Meperidine is the preferred drug for this purpose.

Although toxic effects follow the clinical use of methadone, these are usually less serious than after morphine. Sedation is much less marked than with morphine yet it can be produced with large doses (e. g. 30 mgm. or more in former addicts⁷⁵). Respiratory depression is usually slight after analgesic doses of methadone and it has been used in poliomyelitis patients with spinal and bulbar lesions in whom other analgesics and barbiturates were contraindicated.⁷⁷ The three common complaints after methadone are nausea, vomiting and dizziness (or lightheadedness). They appear in 10-15 per cent of patients in bed. In ambulatory patients their incidence is variable but may be as high as 40 per cent.^{21, 77, 79, 81, 82} All authors agree that there is no true vertigo as shown by ataxia and nystagmus. Infrequent toxic complaints are sedation or pruritus (common after morphine), euphoria, amnesia, headache and dry mouth. Beecher^{76, 86} considered that methadone has no advantage over morphine in respect of the acute toxic effects of single doses. Nausea, vomiting and dizziness are no more frequent than after morphine^{8, 87} and it is likely that extensive controlled experiments with iso-analgesic doses would favor methadone.

Addiction and the development of tolerance to methadone. It was natural that careful studies should be made as early as possible to determine the likelihood that methadone will cause addiction. Meperidine, a much less potent analgesic drug, has caused primary addiction and is an imperfect substitute for morphine in persons addicted to the latter. Primary addiction to methadone has not yet been reported. However, specialized research has shown that some features of addiction with physical dependence are common both to morphine and methadone. Tolerance appears to accompany genuine addiction. Although the exact relationship of the two phenomena is obscure, tolerance to methadone will also be discussed.

Experimental studies in animals indicate that repeated doses of methadone do not lead to serious addiction. Scott, Chen and their colleagues²⁸ observed that the duration of analgesia in rats on a fixed dose of methadone diminished after repeated daily doses and that the

lethal dose of the drug (LD₅₀) was increased after 27 days. Tolerance of sedative and analgesic effects was observed in dogs; the only evidences of physical dependence after withdrawal of methadone were tachycardia and slight fever. The dogs of Wikler and Frank⁸⁸ developed a similar tolerance but had more striking withdrawal symptoms which the authors described as more abrupt and more severe than those after morphine but shorter in duration. Finnegan and others⁸⁹ also used dogs which became tolerant of the hyperglycemic action of methadone. Acute tolerance of the hypotensive action of methadone and other analgesics³⁴ has already been described. The study of Woods, Wyngaarden and Seevers⁹⁰ was made in monkeys which are superior animals for the investigation of addiction. Morphine and methadone were compared simultaneously. Both drugs initially caused salivation, lacrimation, mydriasis, muscular weakness and pronounced respiratory depression. Whereas tolerance of the depressant action of morphine progressed so that the daily dose could be increased thirteen-fold, none could be detected after methadone, the fixed dose of which sometimes caused greater depression later in the experiment. Characteristic withdrawal symptoms were observed only after morphine. Crossed tolerance was slight (methadone to monkeys after morphine) or absent (morphine to methadone-treated monkeys). These experiments with monkeys are the most important animal experiments cited and suggest that addiction in man should be slight.

Clinical tests in which primary interest was in analgesia sometimes revealed tolerance so that increased doses were needed to secure the same relief from pain.^{15, 77} On the other hand, Houde and others¹⁵ mention cancer patients who received the drug for 18-127 days with no evident tolerance, and Popkin's patients, treated for months, showed little tolerance and no signs of addiction.⁸² He described one patient who required 135 mgm. a day for several weeks after which the dose was gradually reduced; the drug was completely discontinued after 6 months.⁹¹ Lastly, euphoria which is common after morphine and presumably would facilitate habituation, is only infrequently observed in patients receiving methadone.

That methadone has definite but moderate addicting potentialities was convincingly shown by the special studies of Isbell and his co-workers^{72, 75, 92} using morphine addicts or former addicts as experimental subjects. Levo-methadone accounted for all the effects of race-

mic methadone which is the drug ordinarily used.⁷² Large single doses of methadone (15-30 mgm.) administered to former addicts imitated the effects of morphine such as decreased respiratory rate, moderate bradycardia, lowered body temperature and slight fall in blood pressure. Large doses, divided over hours, caused pronounced sedation without, however, altering the blood sugar level. Former addicts are specially conditioned to recognize the euphoric effects of a morphine substitute. Although these subjects considered methadone inferior to morphine in this regard, yet they found it a very satisfactory drug. Euphoric effects were produced by 30 mgm. or more subcutaneously; extreme euphoria was reported after intravenous doses of 10-30 mgm. The authors concluded that addicts and former addicts would go to great lengths to secure methadone if morphine could not be obtained.⁷⁵

Numerous observations were made after repeated doses of methadone had been given to morphine addicts or former addicts. Members of the latter group in whom tolerance and withdrawal symptoms were studied received subcutaneous doses of methadone four times daily for 1-6 months. The maximum dose temporarily reached for one subject was 200 mgm. for each dose (800 mgm. in 24 hours); such doses had to be reduced owing to pronounced narcosis, anemia, jerking movements during sleep, etc. The dose ordinarily reached was about 50 mgm. (200 mgm. in 24 hours). Tolerance to the following effects of methadone were noted: analgesia (method of Hardy, Wolff and Goodell), sedation, anorexia and miosis. Partial tolerance to the respiratory and circulatory effects of methadone was present. Quantitative differences from the picture in morphine-tolerant subjects were noted. In morphine addicts methadone could be substituted for morphine and the change could not be recognized by the subject (1 mgm. of racemic methadone for each 4 mgm. of morphine.)

Withdrawal symptoms are used to measure the degree of physical dependence on drugs used as substitutes for morphine. A comparison is made with similar symptoms after morphine withdrawal as measured by Himmelsbach's point-scoring system.¹¹ In comparison with morphine, the abstinence-syndrome of methadone was mild, being characterized by weakness and fatigue, anxiety and insomnia, abdominal discomfort, slight loss of weight, slight fever, and tachycardia with some elevation of the systolic blood pressure. The syndrome appeared more slowly and reached its peak later than after morphine-withdrawal

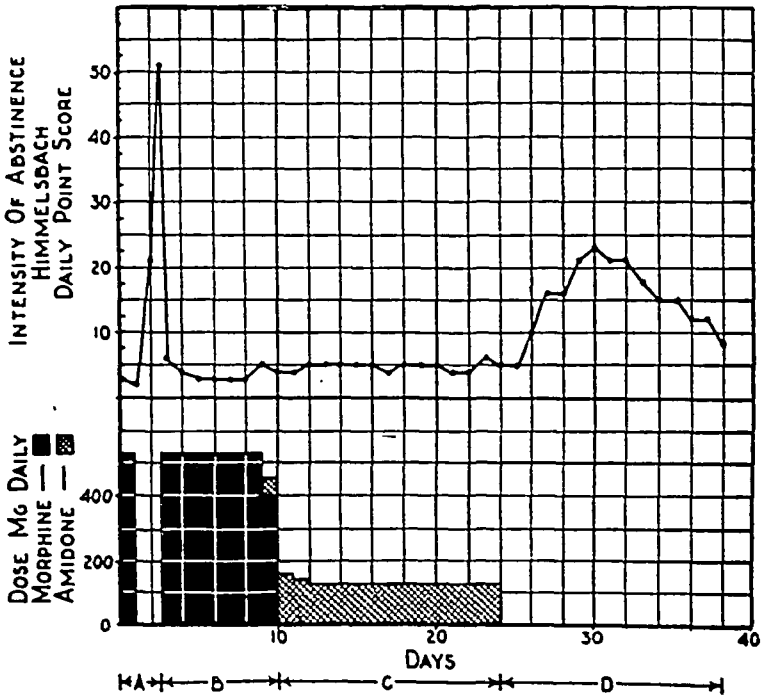


Figure 3

A. Withdrawal syndrome of morphine (control); C. substitution of methadone for morphine; D. withdrawal syndrome of methadone. Note that methadone is a satisfactory substitute for morphine in the addict and that the withdrawal syndrome of methadone is much less severe and reaches peak intensity more slowly than that of morphine. Other experiments demonstrated that the abstinence symptoms disappeared more slowly after methadone-withdrawal. (From Isbell and others,⁷² *J.A.M.A.*, 1947, 135:888.)

(Fig. 3). Thus when methadone is repeatedly administered in suitable doses as a substitute for morphine in addicts or to produce addiction in former addicts, its withdrawal is followed by symptoms much less severe than after morphine-withdrawal. Hence physical dependence on methadone is definite but mild in *such human subjects*. In normal patients evidence of addiction to methadone has been difficult to secure.^{77, 79, 81} Isbell and his colleagues reported that "mild signs possibly indicative of developing physical dependence" were observed in 2 cancer patients following the abrupt withdrawal of methadone which had been administered for 35-40 days. Withdrawal was later repeated without increase of withdrawal symptoms and none was observed in

17 other patients receiving the drug for 3-25 weeks. Methadone is probably the best drug available to break addiction to morphine; it can be substituted for morphine in one-fourth the dose of the latter and then withdrawn abruptly with a much less stormy abstinence period than after morphine-withdrawal.

Summary. Methadone is a synthetic analgesic drug with a potency equal to or somewhat greater than that of morphine. Pharmacologically it has a remarkable resemblance to morphine. Analgesic doses of methadone compared with morphine cause less sedation, less respiratory depression and euphoria less frequently. It appears not to cause constipation. Small doses successfully combat cough. It is effective by mouth. With the exception of (1) pre-anesthetic medication for which the sedative effects of morphine are desired and (2) analgesic medication in labor for which meperidine is much more suitable, methadone appears to be useful in any clinical situation demanding the relief of pain. The toxic complications of the therapeutic use of methadone are not serious and possibly occur less frequently than after morphine; this is clearly the case with reference to addiction *in normal patients*. On the other hand, since morphine addicts or former addicts can use methadone with nearly the same satisfaction they derive from morphine, rigid legal control of the distribution of methadone is necessary. Methadone is the best available drug to which to transfer morphine addicts before abrupt withdrawal since the abstinence syndrome after methadone is mild and the doses need not be too large. Methadone is the most desirable analgesic for the treatment of pain in the chronically ill provided that a drug as powerful as morphine is required.

Conclusions. Meperidine (Demerol) and methadone (Dolophine, Adanon) are useful substitutes for morphine. Meperidine is the best drug for obstetrical analgesia for which neither morphine nor methadone is safe. The antispasmodic and atropine-like effects of meperidine are not sufficiently impressive to favor it in comparison with methadone. Unlike morphine, analgesic doses of meperidine or methadone cause little or no respiratory depression, little sedation, euphoria only infrequently and no constipation. The toxic effects of either drug are rarely serious and perhaps no more frequent than after morphine. Both drugs have a low addiction-liability whereas that of morphine is high.

Full evaluation of the advantages described for metopon awaits further work. It is not known whether it has significant advantages

over dihydromorphinone (Dilaudid). Its addiction-liability with associated tolerance is probably high in comparison with meperidine or methadone.

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Addendum: Newer Synthetic Analgesics (*Ann. New York Acad. Sc.*, 1948, 51, 1-174) was published after this article was in press. Only two of the manuscripts of this publication were available to the author.

EARLY AMBULATION FOLLOWING SURGICAL PROCEDURES*

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I^N the past five years, early postoperative ambulation has evolved from the status of a clinical experiment to that of an established conservative routine. It ranks as an advance in therapy, not because it is an entirely new concept, but because it has recently become so widely accepted. It has been used informally for years in isolated instances when patients could not be confined to bed, as in children's hospitals and in outlying areas where early evacuation of patients has been necessary because of limited facilities.

In 1899 Ries,¹ a Gynecologist in Chicago, was the first to report on the benefit of early rising after surgical procedures. At that time American Surgeons paid little attention to this contribution, but in Continental Europe, early rising was reported in 1909 and since that time has been enthusiastically used by many European clinics.

Early Ambulation was reintroduced in this country by Dr. Leithauser of Detroit, who published a report in 1941.² The value of the method was brought to Dr. Leithauser's attention by a young man on whom he had done an appendectomy in 1938. The patient insisted on going home on his first postoperative day. On the next day, he drove 30 miles into town to do some shopping. He passed the following days by working in his garden. When he strode into Dr. Leithauser's office after a 40-mile drive on the fifth postoperative day, Dr. Leithauser was impressed with the most apparent effect of early ambulation. This was the patient's rapid return of strength and free activity. Following Leithauser's report, there have been many other reports in the literature on early postoperative rising and there have been frequent references to the fact that early rising is routinely practiced by the authors of papers on other surgical subjects.

* Read October 12, 1948, before the 21st Graduate Fortnight of The New York Academy of Medicine. From the Surgical Service, Peter Bent Brigham Hospital, Boston, Massachusetts.

The biological experimental data in early postoperative activity are of interest because they indicate that wound healing is not retarded by early activity. It appears too, that the general nutrition and health of an animal is better, if early postoperative activity is permitted.

Newburger³ studied rats. He found that the tensile strength of their wounds was greater, if postoperative activity was allowed.

Recently Royster, McCain and Sloan⁴ published a study on a series of dogs. After similar surgical procedures, one group of dogs was confined in cages and the other group was exercised. They report no observable difference in the rate of wound healing as measured by the tensile strength of the wounds at various postoperative periods. They observed that the unexercised dogs tended to lose weight and appeared in poorer condition, but the exercised dogs remained in good condition and occasionally gained weight.

At the Peter Bent Brigham Hospital our experiences with early rising began in the middle of 1942 when we undertook a clinical study of this method.

For purposes of definition, early rising means getting out of bed and walking two or three times either on the day of the operation or on the following two days. The majority of our patients are gotten up on the day after operation. In order to make the study as revealing as possible, patients with all types of operative procedures were allowed to get up except those with generalized peritonitis. As we study this group of patients, our conclusions as to the results of the method are drawn from clinical impressions gained in observing early and late rising patients and from controlled statistical data on the measurable complications, such as atelectasis, phlebitis, wound infection, wound disruption, and the recurrence rate of hernia.^{5,6} In the course of the study, we have also acquired some definite ideas on how early ambulation is most effectively carried out and what its limitations are.

Clinical observations reveal the most striking benefits of early ambulation. The early rising patients have a definitely more rapid return to normal strength and activity. Their outlook and morale are better. Patients who are gotten up are less impressed with how sick they are and they are more willing to move about in bed and to assist with their own care. Particularly in men who are allowed to stand to void, there is a lower incidence of urinary retention. One gains a distinct impression that wound pain is reduced at an earlier time among the early rising patients.

On about the fourth postoperative day, they move around quite freely and need no assistance in getting in or out of bed and rarely need medication for pain. About this time, they often ask how soon they may be discharged and there is occasionally some difficulty in convincing patients that they should stay in the hospital for the period of a week after a major abdominal procedure. At the time of discharge, the patients are strong and essentially well. I do not mean that these patients can immediately return to full activity, but it is clear that early ambulation prevents the marked loss of strength that occurs with continued bed rest, and that it definitely shortens the period of convalescence.

Two interesting and unforeseen sidelights have appeared as a result of instituting early ambulation. First we find that our present hospital architecture is inadequate to meet the increased demand on the ward lavatories. Plans for new building in our own hospital and in other hospitals must include more lavatories per bed. An important corollary to this is that the nursing service has been relieved of a considerable amount of postoperative bedside care. The second sidelight is that there has been so much more visiting between rooms, that it was necessary for the administrative authorities to relax an old hospital rule against this practice.

In order to study the effects of early rising on the incidence of postoperative complications, a series of patients was chosen in which the incidence of postoperative complications is highest, that is, patients with operations in which the peritoneal cavity has been opened. These include major intraabdominal operations and herniorrhaphies of various types. These patients were all operated upon at the Peter Bent Brigham Hospital. Interrupted silk or cotton sutures were used except in the peritoneum where a continuous suture of chromic catgut was used, size double zero to number one. The test series consisted of 504 such cases in which early rising was practiced. The control series is comprised of 680 cases, all of whom remained in bed for at least seven days after operation. The postoperative complications to be reported are atelectasis, phlebitis, wound infection, and wound disruption.

It has been stated that early rising reduces the incidence of both atelectasis and phlebitis; our figures do not substantiate that claim.

Table I is a comparison of the incidence of atelectasis in our two groups. It is seen that the incidence of atelectasis among the late rising group is 6.2 per cent and among the early risers it is 6.3 per cent. When

TABLE I—ATELECTASIS
(Major Abdominal Procedures and Herniorrhaphies)

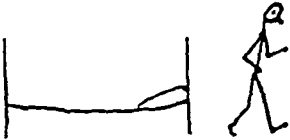

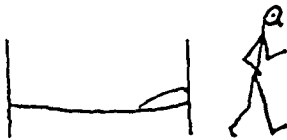

	Number of Cases	Atelectasis	
		Number	Per Cent
Early Risers 	504	32	6.3%
Late Risers 	680	42	6.2%

TABLE II—PHLEBITIS
(Major Abdominal Procedures and Herniorrhaphies)

	Number of Cases	Phlebitis	
		Number	Per Cent
Early Risers 	504	10	2.0%
Late Risers 	680	13	1.9%

these figures are cross analyzed for age of patient, type of anesthesia, and site of the incision, no significant difference in the incidence of atelectasis between the two groups can be shown. It would appear, therefore, that early rising does not exert a significant effect on the factors which produce or prevent atelectasis.

Table II shows that the incidence of thrombophlebitis of the deep

TABLE III—WOUND INFECTION
(Major Abdominal Procedures and Herniorrhaphies)

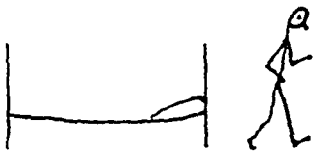

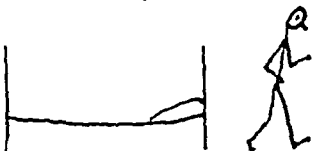



	<i>Number of Cases</i>	<i>Wound Infection</i>	
		<i>Number</i>	<i>Per Cent</i>
<p>Early Risers</p> 	504	14	2.8%
<p>Late Risers</p> 	680	30	4.4%

TABLE IV—WOUND DISRUPTION
(Major Abdominal Procedures)

	<i>Number of Cases</i>	<i>Wound Disruption</i>	
		<i>Number</i>	<i>Per Cent</i>
<p>Early Risers</p> 	243	3	1.2%
<p>Late Risers</p> 	443	12	2.7%

veins of the legs in the late rising groups was 1.9 per cent as compared with 2.0 per cent in the early rising group. Cross analysis, to include other factors of possible bearing, fails to show any significant difference between the two groups. So it appears that early rising has no demonstrable effect on the factors which produce postoperative thrombophlebitis.

TABLE V—HERNIA RECURRENCE
(Indirect Inguinal Hernias)

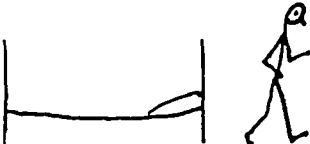

	<i>Number of Cases</i>	<i>Recurrences</i>	
		<i>Number</i>	<i>Per Cent</i>
Early Risers 	162	5	3.1%
Late Risers 	150	6	4.0%

We were interested in whether early rising would have any influence on wound complications. The incidence of wound infection (Table III) was 4.4 per cent in the late rising group, compared with 2.8 per cent in the early rising group. It is hard to imagine how early rising would reduce wound infection, but it can be stated with assurance that early rising does not increase the incidence of wound infection.

Whether early rising would have a weakening effect on wounds was a matter of some early concern. If it does weaken wounds, this should be apparent in an increased incidence of postoperative wound disruption. Since wound disruption occurs more commonly in abdominal operations, as opposed to herniorrhaphies, only the abdominal operations are compared in studying the influence of early rising on wound disruption. Table IV shows that among the late rising group, the incidence of wound disruption was 2.7 per cent whereas, in the early rising group, the incidence was 1.2 per cent. These cases were cross analyzed for the influence of the site of operation, age of patient, and type of anesthesia. It does not appear that early rising increases the incidence of postoperative wound disruption.

To further study the effect of early rising on wound healing, we were interested to see whether there would be an increase in the incidence of hernia recurrences. In this phase of the study we now have follow-up data on a total of 421 inguinal herniorrhaphies. The follow-up

TABLE VI—HERNIA RECURRENCE
(Direct Inguinal Hernias)

	<i>Number of Cases</i>	<i>Recurrences</i>	
		<i>Number</i>	<i>Per Cent</i>
<p>Early Risers</p> 	53	5	9.4%
<p>Late Risers</p> 	56	7	12.5%

interval varies from six months to six years with an average of two years. Table V shows that in indirect inguinal hernia, the recurrence rate is 4.0 per cent among the late risers, compared with 3.1 per cent among the early risers. In cases of direct hernia, the recurrence rate is known to be higher. Table VI shows that in our cases of direct hernia, the recurrence rate among the late risers was 12.5 per cent, whereas, the recurrence rate in the early rising group was 9.4 per cent. When these figures are cross analyzed for the type of operation, type of anesthesia, and age, it could not be shown that early rising increased the incidence of hernia recurrence.

The foregoing data and our clinical experiences have given us some definite ideas about the practice of early rising and its limitations. It is evident that there is nothing magic in the act of getting a patient out of bed. One would not expect much to be accomplished for the patient, if he is only assisted out of bed, to stagger to a chair, and sit there until someone remembers to put him back.

Rising and walking should be just a part of an over-all program to rehabilitate the postoperative patient. Briefly our general procedure is as follows: Before operation, we explain to the patient that postoperatively, certain activities are beneficial and will be encouraged. He is told that he will be asked to take deep breaths and to turn over at

intervals even though this may be uncomfortable. He is taught the technique of getting out of bed and also a group of leg and foot exercises. At this time he is advised to practice using the urinal in bed for the purpose of breaking the reflex inhibition against voiding in bed which he was taught in childhood.

After operation, he is turned over at least every two hours. When he is conscious, he is reminded to take one or two deep breaths every five minutes. He is urged to exercise his feet and legs about twenty times each hour. These exercises consist in strong dorsiflexion and plantar flexion of the feet and toes and flexion of the knees and hips. When the patient is gotten out of bed, it is done in such a manner as to put a minimal strain on the muscles in the region of the operation. The patient is turned onto the side of his operation, he flexes his hips and knees which brings his lower legs to the edge of the bed. He is then assisted up sidewise to a sitting position on the side of the bed.

It is considered important that patients wear the same height heels as usual when they walk after operation. This is particularly so in women who may have tight heel cords. Walking in flat slippers might strain the small plantaris muscle and initiate a pathological sequence which would result in deep leg vein phlebitis. As the patient stands erect, he is encouraged to take deep breaths and to cough several times. This is designed to rid his bronchial tree of any secretions which may be present. He is then encouraged to walk some ten to thirty feet and allowed to sit in his chair for no longer than it takes for the nurse to straighten the bed. He then takes another short walk and is put back into bed, repeating in reverse, the steps of rising. The patient is gotten out of bed and exercised two or three times during the first day. With each rising, his strength and confidence increase. He is not allowed to sit in the chair more than five minutes at a time. If he wishes to stay out of bed, he is advised to get up from the chair and to walk about every five minutes. The reason for limiting the period of sitting down is that this sitting position encourages venous stasis and may well lead to thrombosis, if long intervals of sitting in a chair are permitted. As soon as practical, the patient is allowed to go to the bathroom, which obviates the need for bedpans. About the fourth day, the patient is able to get out of bed himself and begins to take part in the small but definite social life of the hospital.

After six years of experience with early ambulation, we believe that

it is a desirable method of postoperative care. It prevents the onset of weakness which comes with prolonged bed rest. It definitely accelerates the rate of return to normal health. Wound pain appears to be diminished in degree and extent. The required nursing care is less and the patient is more independent. Our statistical data do not show that early rising reduces the incidence of atelectasis or phlebitis, but it does show that early rising has no apparent ill effect on wound healing, as demonstrated by the fact that there is no increase in the incidence of wound infection and wound disruption, or in the recurrence rate of hernia.

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PRINCIPLES OF NUTRITION THERAPY*

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THE FOUR cardinal principles of nutrition therapy are (1) early treatment; (2) the use of therapeutic amounts of prescribed nutrients; (3) the provision of all of the nutrients necessary for life and health in effective quantities and in forms utilizable by the patient; and (4) continuous and prolonged treatment.

A nutritional disorder may be primarily of dietary origin or it may be secondary to some other disease or condition that interferes with the assimilation or utilization of foods, or increases requirements. Definition and correction of the underlying cause should be attempted in every case. In one instance, major hope for permanent recovery may be in education of the patient on proper dietary habits while, in another, cure may depend to a considerable extent upon the success of some surgical procedure or the healing of some infectious process.

Most nutritional disorders become increasingly resistant to therapy as they increase in chronicity and in severity. They are most susceptible to correction before anatomical lesions develop. The importance of early treatment, therefore, cannot be over-emphasized. In the field of nutrition, as much as in any other branch of medicine, an ounce of prevention is worth a pound of cure.

Early treatment implies early diagnosis, often a difficult task. The anatomical signs recommended by Jolliffe,¹ Kruse and others² for the diagnosis of deficiency states are of value and should be known to every physician, but the presence of any of them, when due to a nutritional deficiency, indicates a deficiency of some duration. Functional disturbances such as anorexia, irritability, apathy, constipation, diarrhea and muscle cramps are earlier but less reliable indicators of nutritional disorder. Whole blood and serum levels of the vitamins and urinary excretion tests generally reflect the recent intake of the substance tested, not

* Read October 11, 1948 before the 21st Graduate Fortnight of The New York Academy of Medicine.

TABLE I

FOOTNOTES TO RECOMMENDED DAILY DIETARY ALLOWANCES

Revised 1948

Food and Nutrition Board, National Research Council

1. Objectives toward which to aim in planning practical dietaries: The recommended allowances can be attained with a good variety of common foods which will also provide other minerals and vitamins for which requirements are less well known.
2. Calorie allowances must be adjusted up or down to meet specific needs. The calorie values in the table are therefore not applicable to all individuals but rather represent group averages. The proper calorie allowance is that which over an extended period will maintain body weight or rate of growth at the level most conducive to well-being.
3. The allowance depends on the relative amounts of vitamin A and carotene. The allowances of the table are based on the premise that approximately two-thirds of the vitamin A value of the average diet in this country is contributed by carotene and that carotene has half or less than half the value of vitamin A.
4. For adults (except pregnant and lactating women) receiving diets supplying 2000 calories or less, such as reducing diets, the allowances of thiamine, and niacin may be 1 mg. and 10 mg. respectively. The fact that figures are given for different calorie levels for thiamine and niacin does not imply that we can estimate the requirement of these factors within 500 calories, but they are added merely for simplicity of calculation. In the present revision, riboflavin allowances are based on body weight rather than calorie levels. Other members of the B complex also are required, though no values can be given. Foods supplying adequate thiamine, riboflavin, and niacin will tend to supply sufficient of the remaining B vitamins.
5. There is evidence that the male adult needs relatively little iron. The need will usually be provided for if the diet is satisfactory in other respects.
6. The need for supplemental vitamin D by vigorous adults leading a normal life seems to be minimum. For persons working at night and for nuns and others whose habits shield them from the sunlight, as well as for elderly persons, the ingestion of small amounts of vitamin D is desirable.
7. During the latter part of pregnancy the calorie allowance should increase approximately 20 percent above the preceding level. The value of 2400 calories represents the allowance for pregnant, sedentary women.
8. Allowances for children are based on the needs for the middle year in each group (as 2, 5, 8, etc.) and are for moderate activity and for average weight at the middle year of the age group.
9. Needs for infants increase from month to month with size and activity. The amounts given are for approximately 6 to 8 months. The dietary requirements for some of the nutrients such as protein and calcium are less if derived largely from human milk.

the nutritional health of the body. Plasma proteins, calcium and phosphorus tend to remain within normal limits in malnutrition unless the body is severely depleted of these substances. The existence of a nutritional anemia indicates a relatively long standing and severe depletion of some substance necessary for hemapoiesis.

The finding of a negative nitrogen or calcium balance is reliable evidence of an unfavorable state in protein or calcium metabolism. A positive balance in relation to either of these substances, however, is not by itself reliable evidence of a satisfactory state of protein or of calcium nutrition.

Obviously the diagnosis of early nutritional deficiency states requires the exercise of considerable judgment and diagnostic acumen on the part of the attending physician. It requires careful appraisal of the patient's medical and dietary history as well as of his symptoms and signs. For sound judgment regarding the need for preventive measures, the medical and dietary histories are all important. If the apparently healthy person's diet fails to meet the allowances for specific nutrients recommended by the Food and Nutrition Board of the National Research Council,³ Table I, it is generally wise for the physician to bring it up to and maintain it at least at this level. The caloric intake, of course, needs to be adjusted to the demonstrable needs of the patient.

The Recommended Dietary Allowances of the Food and Nutrition Board are designed to meet the requirements of the vast majority of healthy persons. Many individuals may get along quite satisfactorily on lesser amounts of certain nutrients but, as it is not feasible for the physician to attempt to determine even the approximate nutritional requirements of his patients, except for calories, and as there is evidence that both animals and man may benefit by the regular ingestion of more than minimal amounts of most nutrients other than calories, it is sensible to err in favor of the patient. Further, the physician has an obligation to his patient to make full, intelligent use of the tools at his disposal. In most nutritional disorders for which direct, immediate therapy is available, he is no more justified in depending solely upon repeated dietary advice than he would be in refusing to consider insulin therapy for a patient with uncontrolled diabetes mellitus, on the grounds that strict adherence by the patient to a rigid dietary regimen probably would result eventually in control of the diabetes.

A sharp distinction must be made between the prevention of nutri-

tional deficiencies and the cure of existing nutritional deficiency states. The most efficient therapeutic amounts of the vitamins generally range from five to ten times maintenance amounts. However, there is considerable variability. In chronic vitamin A deficiency, daily doses of 100,000 to 150,000 I.U. of vitamin A are frequently necessary, while in vitamin C deficiency in the adult as little as 150 mg. of ascorbic acid daily may be curative. The intensity of treatment also will vary with the severity of the deficiency state exhibited by the patient and with the physician's estimate of the extent to which the patient's tissues are depleted. I believe it to be advantageous to replenish depleted tissue stores as rapidly as possible and that this procedure hastens the recovery of the patient. It is good practice never to initiate vitamin therapy with daily amounts of the vitamins smaller than five (5) times the Recommended Dietary Allowances. The water soluble vitamins, whether given by mouth or parenterally, always should be administered in divided doses throughout the day to prevent excessive waste by spill over into the urine.

The protein needs for depleted tissues are considerably greater than those for maintenance, however, data are still meager regarding the quantitative needs for effective tissue repletion. Generally, amounts of protein ranging from two (2) to three (3) times the Recommended Dietary Allowances have been found to be effective as well as practical; 125 grams daily might well be regarded as the minimal therapeutic dose in the adult, to be attained as early as possible in the course of any disease or condition associated with increased protein catabolism. Unless muscle tissue is so considered, the body has no protein reserves and, under pathologic conditions, the loss of protein may be large, up to several hundred grams a day.

Except under experimental conditions, man never develops a deficiency of one nutrient without an associated deficiency of others. Because of the unequal distribution of nutrients among foodstuffs, differences in requirements and in the susceptibility of different tissues, it is the rule for the deficient patient to demonstrate a predominance of the lesions of one, two or three deficiencies, over any of the others. It would be a serious mistake for the physician, however, ever to assume that a single deficiency exists and to attempt therapy with a single nutrient.

The various nutrients essential for life and health are effective only through the action of one upon another. Activators require other activa-

tors, mediators and substrata. It is also true that the absolute requirement for some nutrients is decreased in the presence of ample amounts of certain others and that variations in the composition of the diet may alter requirements. The need for preformed niacin is less when there is ample tryptophane in the diet and a high fat diet may increase riboflavin and decrease thiamine requirements.

The effects of such factors cannot be determined quantitatively by the practicing physician. For optimal growth and welfare, it is desirable for him to provide all necessary nutrients in reasonably ample amounts. The chain is no stronger than its weakest link and the physician should make every effort to ensure that each link is sufficiently strong for the load required of the chain.

At least eight (8) amino acids (lysine, tryptophane, phenylalanine, leucine, isoleucine, threonine, methionine and valine) are essential for man. In the absence of any one of these, all the others become useless for the purpose of tissue synthesis. The body apparently discards all essential amino acids not immediately utilizable and waits for the simultaneous delivery of a complete assortment before starting the synthesizing process.⁴ Obviously, then, the nutritional value of any protein or combination of proteins is determined largely by its content of essential amino acids. Its ability to promote tissue synthesis is limited by that essential amino acid available to the body in smallest amount relative to need.

For the efficient utilization of dietary protein for body building, the protein consumed at each meal period should be complete, i.e., contain all of the essential amino acids in optimal amounts. Practically, this means simply that the physician should see to it that his patient receives a fair amount of protein of animal origin at every meal. If the total quantity of food consumed is unusually small and it becomes necessary to make a choice, vegetable sources of protein should be dispensed with rather than high quality animal proteins which are more dependable sources of the essential amino acids.

When sufficient amounts of high quality protein cannot be ingested in the form of customary foods, there is available a variety of protein concentrates such as egg white, powdered whole egg, casein, and hydrolyzed proteins. The physician should ascertain that the amino acid composition of the hydrolyzed protein of his choice is adequate and that at least 50 per cent of it consists of single amino acids. The adequacy of

a hydrolyzed protein can be determined by the ability of the preparation to support normal growth in immature rats or to produce weight gain in protein-depleted adult rats when fed as the sole source of protein.^{5, 6, 7}

Tissue proteins cannot be formed unless energy is available. With the available energy from fat and carbohydrate below a maintenance level, some protein must be utilized as a source of energy, thus diminishing the amino acids available for tissue synthesis. With adequate calories from other sources, the degree of protein utilization for tissue synthesis is proportional to the protein intake. An increase in the caloric intake above the critical level, however, does not result in any increase in the utilization of protein. All that results is a deposition of fat. The critical caloric level for the physically inactive, afebrile man appears to be about 1500-1800 calories per day.⁸ In addition to adequate protein and calories, adequate amounts of the vitamins, particularly those of the B complex, are necessary for tissue synthesis.

Physicians, nutritionists and dietitians have become accustomed to talk of balanced diets, a term which seems to mean different things to different people and means nothing to me. The ratio of one nutrient to another in the diet is not a thing of prime importance. Fat does not burn in the flame of carbohydrate. The important thing is that there be enough of each and everyone of the necessary nutrients. The calcium/phosphorus ratio in the diet assumes importance only when the content of either one of them is minimal. When the content of each of them is one gram or more, the quantitative relationship one bears to the other is of no consequence.⁹ Nutritionally effective amounts of one nutrient do not cause the development of deficiencies in another, provided that all are present in amounts sufficient to meet metabolic requirements. The presence of an extraordinarily strong link does not weaken the chain, though a load calculated on the strength of such a link is apt to break the chain.

For the treatment of any nutritional deficiency, it is recommended that the patient receive definitely therapeutic amounts of those nutrients the deficiency of which is considered to be the cause of the patient's presenting signs and symptoms, and protective amounts (more than the Recommended Dietary Allowances) of all other necessary nutrients; with the caution that there is nothing to be gained by overtaxing the physiological capacity of the calorically underfed person to form useful,

functional tissue by too strenuous a regimen of high caloric feedings. The proper treatment of obesity calls for a diet deficient only in calories and containing protective amounts of protein and of the vitamins.

Whenever it is possible for the patient to ingest and assimilate sufficient nutrients, the oral route of administration is the route of choice. If it becomes necessary to give vitamins parenterally, intramuscular injection should receive first consideration. If the intravenous route seems to be the only practical method, the vitamins should be given in divided doses throughout the day or should be incorporated in slow infusions. The rapid intravenous injection of the water soluble vitamins is accompanied by considerable waste due to spill over into the urine. Intrathecal administration is never necessary.

The enteral administration of protein (by mouth, stomach tube or jejunostomy) is much to be preferred over the intravenous route, the only feasible parenteral route, as it is difficult to administer sufficient protein and calories intravenously to effect tissue repletion without simultaneously administering an excess of fluid. In addition, all parenteral injections are expensive, unpleasant and not without danger. There is a place in medicine, however, for intravenous protein feedings and their use, when indicated, constitutes a great improvement in the care of patients.

Parenteral sources of protein may consist of whole blood or plasma or amino acid mixtures such as hydrolyzed proteins. In general, whole blood is indicated when there has been an external loss of blood or in inflammatory, infectious or other conditions where there is a hemoglobin deficit. Therapy with plasma is desirable where there has been a loss of plasma with resultant hemoconcentration, as in burns, intestinal obstruction and peritonitis and extensive extravasation from wounds.

In contrast to their value for the replacement of blood losses or for the correction of anemia, whole blood and plasma as sources of parenteral protein food are both expensive and unphysiological. The injection into the blood stream of an appropriate mixture of amino acids is a physiological method of alimentation. This is how ingested protein reaches the tissues. Injected amino acid mixtures supply to the tissues the building stones of protein and thus help to prevent tissue depletion.

Proper nutrition therapy implies continuous and prolonged treatment. The initial stages of recovery from deficiency states may be strikingly rapid or very gradual, depending upon the duration and

severity of the deficiency, but convalescence is generally protracted and relapses are common. The initial intensive period of therapy should be followed by a much longer period of less intensive but fully comprehensive therapy and the patient should be continued on protective amounts of the essential nutrients for at least one year following apparently complete recovery. His dietary intake of specific nutrients should never be permitted to drop below the amounts listed in the Recommended Dietary Allowances of the Food and Nutrition Board.

The basic principles of nutrition therapy are readily summarized in five words: "Early," "Enough," "Complete," "Continuous" and "Prolonged." To the extent that the physician is able to apply all of these principles in the nutritional management of his patients, to that extent will he be successful in their nutritional rehabilitation.

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PROGRESS REPORT

THE FRIENDS OF THE RARE BOOK ROOM
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THE NEW YORK ACADEMY OF MEDICINE, INC.

THE Library of The New York Academy of Medicine ranks as one of the five great medical libraries of the world. This remarkable collection of books serves as the focal point of medical learning for the metropolitan area and attracts to its reading rooms scholars, practitioners and students in large numbers.

The maintenance of the library is costly, and the effort to keep up to date on current books and periodicals has made it necessary to institute strict economy in adding to the unique collections housed in the Rare Book Room. Constantly adding to the store of manuscripts and rare medical books is not only indispensable for historical research, but is likewise important for the prestige of the library. To take advantage of book sales and auctions the Librarian must be assured of the necessary funds. Realizing this, a group of the Fellows of the Academy organized in 1946, "The Friends of the Rare Book Room of the Library of The New York Academy of Medicine" which functions independently but with the endorsement of the Academy Council. The aim is to collect funds annually, adequate for the purchase of such items as the Librarian deems desirable for the Rare Book Room.

The Friends also seek to stimulate gifts of money and books to the Rare Book Room from the general public and hope through an annual lecture by a distinguished scholar to develop interest in books and related fields among the Academy Fellows and the laity. In a general way the Friends have followed the example set by similar groups organized to support other famous libraries. The success already attained in these endeavors can be judged from the fact that in less than three years the organization has collected over \$7000 from its members and an ever-growing lay contingent, known as the "Friends of the Friends." With these funds twenty-four separate purchases of unique old volumes have been made, including the invaluable Bard Collection of auto-

graph letters noted in an earlier issue of the Bulletin. By maintaining a reserve fund the Friends are enabled from time to time to pick up worthwhile items at unusually favorable terms. In addition, some ninety-five gifts have been made to the Rare Book Room. Among the generous donors of noteworthy books we find the names of Drs. Ralph Colp, Reginald Burbank, Frank B. Berry, Alfred Hellman, Claude E. Heaton, Walter Galland, Bradley Coley, DeWitt Stetten, Judson B. Gilbert, Corneille Heymans of Belgium and Puigvert Gorro of Spain. The presentation of the priceless Edwin Smith Surgical Papyrus to the Library by the New York Historical Society and the Brooklyn Museum was in large measure due to the singlehanded efforts of Dr. Fenwick Beekman, first president of the Friends of the Rare Book Room. Not since the acquisition of the Streeter Collection in 1928 has the Rare Book Room fared so well in new and worthwhile accessions.

Realizing the need for the interpretation of the entire Library as a living, growing organism of wide potentialities, the Board of Directors of the Friends determined in 1948 to found a periodical devoted to the Library and its manifold activities. The purposes of the *Academy Bookman* may be stated simply. It endeavors to acquaint the Academy fellowship with the possessions of the Library, with the work of the staff, and to point out the many ways in which the staff can serve the Fellows. It seeks to promote the gifts of rare books, manuscripts, autograph letters and pictures, since it is believed that fitting acknowledgment of donations will stimulate further generosity.

At the present time the membership of the Friends numbers but a scant one hundred. The Fellows of the Academy are urged to help along the splendid work of this worthwhile group by sending their membership dues (ranging from ten to one hundred dollars annually) to the Secretary, Dr. Frederic D. Zeman, 17 East 89 Street, New York. The success of the Friends to date should insure the attainment of the present goal of five hundred active members.

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THE NEW YORK ACADEMY OF MEDICINE
INSTITUTE ON SOCIAL MEDICINE, 1947

EDITED BY IAGO GALDSTON, M.D.

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CONTENTS

Management of Acute Renal Failure 199
I. Snapper

The Place of Electrolyte Studies in Surgical Patients . . 228
John S. Lockwood and H. T. Randall

Section on Microbiology:

The Rh Factor—General Significance and Meth-
ods of Study, *Philip Levine* 244

Recent Views on the Genetics of the Rh-Hr Blood
Factors, *Herluf H. Strandskov* 249

Medicolegal Aspects of the Rh-Hr Blood Types,
Alexander S. Wiener 255

Appraisal of the Clinical Aspects of the Rh Factor,
Peter Vogel 261

Library Notes:

Recent Accessions to the Library 264

AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

MAILTON ASHFORD, *Editor*

As milk contains large amounts of proteins (35 gm. per L.) and sodium chloride (2.5 gm. per L.), both of which were detrimental for patients with acute nephritis, the classical milk diet was abandoned and a diet poor in protein and poor in sodium chloride was advocated. Shortly after the first World War Volhard⁵ recommended an absolute starvation diet consisting only of 800 cc. of fruit juice for patients with acute glomerulonephritis. In his opinion recovery of the diseased renal parenchyma required absolute rest and for this purpose not only excretion of chlorides, urea and other substances but also of water had to be restricted as much as possible. After the introduction of this starvation diet cases of anuria and of eclampsia in acute nephritis have become extremely rare.

In the last decade the unfavorable side actions of the starvation diet have been emphasized. Insufficient intake of calories increases the catabolism of body proteins which in its turn leads to an increase of the non-protein nitrogen of the blood. On a starvation diet so much body protein is broken down that from this source alone 20 grams of urea are formed daily. Thus in cases of impaired renal function starvation produces enough urea to cause a rise in the blood urea nitrogen of 20 mg. per cent daily in an adult. This is the reason why many clinicians now attempt to avoid starvation. As proteins and salts should be avoided, Borst⁶ has advocated a daily diet consisting of 200 grams of butter and 200 grams of sugar. The butter is first melted, then carefully mixed with the sugar and about 12 grams of flour and some coffee flavor are added. The whole is put into the refrigerator. A teaspoonful of this mixture given in iced condition is palatable, but most patients complain if they have to take 400 grams of this mixture daily. Only patients who have been persuaded to understand the necessity of such a diet may be able to tolerate it. On this diet the body produces only four grams of urea daily. Borst calculates that a patient with no kidney function should live five times as long on such a regime as on a starvation diet. It should also be remembered that toxic substances like potassium which play an important role in uremia, are derived from the endogenous break-down of protein.

Even the Kempner diet⁷ (rice, fruit and sugar) consisting of 460 grams of carbohydrates, 20 grams of protein, 0.2 grams of sodium and 0.15 grams of chloride could be used although it contains more protein than the mixture of butter and sugar as advocated by Borst.

After the most serious dangers have been overcome by the butter-sugar or the starvation regime, a diet providing 2,480 calories with four grams of nitrogen, 1,280 mg. of potassium and 470 mg. of phosphorus has been advocated.

Potatoes (boiled)	100 gms.
Rice, Polished (raw)	50 "
Flour (80%)	100 "
Custard powder	25 "
Cream (20%)	200 "
Butter	100 "
Sugar	100 "
Apples or pears	200 "
Vegetables	100 "
Cocoa powder	10 "
Tea infusion	500 "
Coffee infusion	100 "

As far as our own results are concerned, the following figures may be of some importance. Between April 1943 and December 1944, eleven patients with acute nephritis were treated with low salt diet and fluids ad libitum. One patient died. Between December 1944 and August 1948, nine patients with acute nephritis were treated with a starvation diet of 800 cc. of fruit juices for about one week. Thereafter, low salt, low protein diet was given. Of these patients, two died. It is true that nearly all these patients had already been suffering from acute nephritis for several weeks previous to admission to the Hospital. As a rule, no dietary measures at all had been ordered during this period. Under these circumstances, the treatment of the acute nephritis had to start at a stage when in some cases irreparable changes had already occurred. In any case, the difference between the starvation diet and the more liberal low salt, low protein diet do not seem significant.

The introduction of a starvation diet emphasized for the first time the importance of the restriction of the fluid intake in oliguric or anuric patients, irrespective of the etiology of the renal failure. The ingestion of large amounts of fluid in such cases will easily lead to overloading of the circulation with ensuing lung edema and anasarca.⁵ A liberal ingestion of sodium chloride will favor the development of these dangerous complications still more. In anuria the fluid intake should not exceed 1,000 cc. per day which is sufficient to balance the normal loss of water through skin and respiratory tract. In case vomiting and diarrhea are present, the water intake should be adequately increased. Ingestion

of NaCl may be necessary if chlorides are lost in the vomitus. Acidosis should be combatted with sodium bicarbonate by mouth. In case intravenous treatment of the acidosis is necessary small amounts of 5 per cent sodium bicarbonate solution are preferable because they contain as much base as large quantities of 1/6 mol. sodium lactate solution. The outlook of anuria whether due to acute nephritis or lower nephron nephrosis will be improved considerably if from the beginning a low sodium chloride, low protein diet with restricted fluid intake or a starvation diet of 800 cc. of orange juice or a butter-sugar diet, is prescribed.

Occasionally cases of oliguria or anuria are encountered where dietary treatment alone does not lead to favorable results. Many such patients are admitted with left heart failure and pulmonary edema because in order to bring about diuresis they have been overloaded with fluid and salt. (Leiter *et al*^{sa} Muirhead and Fromm^{sb}). Often they are also in severe acidosis or alkalosis. In order to treat such cases methods have been perfected recently by which, at least temporarily, large quantities of the toxic substances which accumulate in the blood during anuria can be removed. These methods consist of continuous dialysis of the blood either by way of an artificial kidney or by continuous lavage of the peritoneal cavity or even of the intestine. Recently exsanguinotransfusion has been recommended. These methods are applied in the hope that by cleansing the blood of the anuric patient life can be prolonged until the tubules have regenerated and diuresis has been restored. The greatest experience has been collected with the artificial kidney as popularized by Kolff⁹ and with peritoneal dialysis as revived by Fine, Frank and Seligman.¹⁰ Both methods use the same principle. In the artificial kidney the blood is dialyzed in a cellophane or cellulose-acetate tube; in the peritoneal dialysis the peritoneal membrane is used as a dialyzing membrane. Intestinal irrigation and exsanguinotransfusion are other methods for the treatment of acute anuria which are based upon fundamentally different principles.

ARTIFICIAL KIDNEY

History: Abel¹¹ and his co-workers already in 1913 constructed an artificial kidney. They prevented the coagulation of blood by hirudin and dialyzed the blood by letting it run through celloidin tubes which were submerged into a dialyzing fluid. Haas¹² between 1915 and 1928 followed up these experiments using celloidin tubes. He also started

with hirudin but soon recognized that for the dialysis of human blood, heparin had to be used. He actually dialyzed the blood of two uremic patients. Necheles¹³ in 1923 used tubes made of peritoneal membrane and Thalhimer¹⁴ in 1938 cellophane tubes. Both these investigators performed dog experiments only. The first apparatus which could be readily used on patients was constructed by Kolff in 1943.⁹ He could obtain practical results because he could use 1.) Cellophane or the closely connected cellulose acetate (Visking), 2.) Heparin, 3.) A large dialyzing surface, 4.) A dialyzing fluid of correct composition.

Table I shows the differences between the Kolff kidney and its predecessors. Slight modifications of Kolff's apparatus have been published.^{15, 16} Other artificial kidneys have been constructed¹⁷ and the models devised by Murray¹⁸ and by Alwall¹⁹ have actually been used in humans (Table I).

Different investigators used dialyzing solutions of different composition. As brought out by Abel plasma only contains 0.6 per cent of chloride and 0.9 per cent of sodium. If the bathwater contains more chloride than the plasma absorption of excessive amounts of chloride ions takes place. This explains why the use of 0.9 per cent sodium chloride as the dialyzing fluid easily leads to anasarca and pulmonary edema. Kolff's dialyzing fluid (Table II) contains 0.6 per cent NaCl, 0.4 per cent KCl, 0.2 per cent of NaHCO_3 , and 1.5 to 2 per cent of glucose, that is, 383 mg. per cent of chloride (plasma water 370 to 420 mg. per cent), 291 mg. per cent Na (plasma water 340 to 360 mg. per cent), 21 mg. per cent K (plasma water 18 to 22 mg. per cent), and 53 volume per cent of CO_2 (plasma water 55 to 77 volume per cent). The bathwater does not contain calcium because this would be precipitated by the sodium bicarbonate. It follows that during the dialysis in the artificial kidney the blood loses considerable amounts of calcium and calcium gluconate must be repeatedly injected intravenously during the procedure.

Glucose is added in order to make up for the osmotic pressure of the plasma proteins. In patients with edema the glucose withdraws fluid from the blood plasma. At the same time glucose absorbed from the dialyzing fluid into the blood has a definite caloric value. On the other hand, the blood sugar of the patients rises to very high values and in the future this excess of glucose may have to be replaced by a non-dialyzable colloid substance. Until now this has not been possible.

TABLE I—HISTORY OF THE DEVELOPMENT OF THE ARTIFICIAL KIDNEY

<i>Investigator</i>	<i>Material</i>	<i>Surface</i>	<i>Anticoagulant</i>	<i>Capacity</i>
Abel et al. ¹¹ 1913	Celloidin	3,200 sq.cm.	Hirudin	20 gms. NPN in 112 hrs.
Haas ¹² 1915-28	Celloidin	2,160 sq.cm.	Hirudin Heparin	2.7 gms. NPN in 7 hrs.
Neches ¹³ 1923	Tubes of peritoneal membrane	4,000 sq.cm.	Hirudin	
Thalhimer ¹⁴ 1938	Cellophane	4 tubes of 2 x 30 cm.	Heparin	200-700 mgms. BUN in 3-5 hrs.
Kolff ⁹ 1943-44	Cellulose (Viking)	33-50 yds. 20,000 sq.cm.	Heparin	42-141 gms. BUN in 8 hrs.
Murray ¹⁵ 1947	Cellulose (Viking)	12 yds.	Heparin	6.6 gms. NPN in 8 hrs. 49 gms. NPN in 26 hrs.

TABLE II—COMPARISON OF ELECTROLYTES IN PLASMA
AND DIALYZING FLUIDS

	<i>Plasma Water</i>	<i>Kolff⁹ Artificial Kidney</i>	<i>Kolff & Kop Peritoneal Dialysis²²</i>	<i>Tyrode Solution</i>
Na mg.%	313-330	291	291	343
Cl mg.%	340-393	383	383	502
K mg.%	16-20	21	21	11
CO ₂ vol.%	55-77	53	53	27
Ca mg.%	10	—	10	7
Glucose mg.%	100	2,000	2,000	100 plus traces of P and Mg.

Whereas Bywaters and Joekes used the dialyzing solution as recommended by Kolff, Murray dialyzed against a solution containing 0.8 per cent of NaCl, 0.02 per cent of KCl, 0.02 per cent of CaCl_2 , 0.01 per cent of MgCl_2 , 0.1 per cent of NaHCO_3 and 0.1 per cent of glucose. Theoretically this solution contains an excess of chloride ions (Table II). Alwall used 0.9 per cent NaCl as dialyzing fluid.

Results: Kolff has treated thirty-one patients, five of whom survived. Two of the five survivors suffered from acute glomerulonephritis, three from lower nephron nephrosis (hepato-renal syndrome after cholecystitis, mercury poisoning and sulfa-drug anuria). In his opinion, dialysis in the artificial kidney is indicated if the blood urea nitrogen has increased to 160 mg. per cent or if the potassium content of the blood has gone up or if severe acidosis has developed. The dialysis lasts usually between five and fourteen hours. During this period so much urea is removed from the blood that the blood urea nitrogen goes down to 50 or 60 mg. per cent. At the same time considerable quantities of creatinine, uric acid, indican, xanthoprotein products are cleared from the blood and can be recovered from the bathwater.

Two of the ten patients treated by Bywaters and Joekes¹⁵ survived. One patient developed oliguria after an explosion and the urea nitrogen of the blood had gone up to 180 mg. per cent. Three days after the dialysis, diuresis started. The second patient became severely uremic after an operation under myanesin anesthesia, probably due to hemolysis caused by the anesthetic. In this patient uremia developed, although he excreted daily about one liter of urine. On the 26th day after operation the blood urea nitrogen had risen to 200 mg. per cent and the artificial kidney was used. Nine days after dialysis, the urinary output increased considerably and the patient recovered. Two of the patients treated with Murray's artificial kidney survived.¹⁸ The first one was a woman of 26 years who after an abortion developed anuria. On the ninth day the patient was treated with the artificial kidney for one hour, two days later for eight hours and again three days later for seven hours. The patient improved and two days later diuresis set in. The other patient, 40 years old, received a transfusion with incompatible blood. After nine days of anuria she was deeply uremic. Treatment with the artificial kidney for 6 hours resulted in a great improvement. Next day diuresis started and the patient recovered. Table III gives a review of the reported cases of recovery after dialysis in the artificial kidney.

TABLE III—CASES RECOVERED AFTER DIALYSIS IN ARTIFICIAL KIDNEY
RECORDED IN THE LITERATURE

<i>Diagnosis</i>	<i>Anuria</i>	<i>Dialysis</i>	<i>Blood Urea Nitrogen Mg.%</i>		<i>Diuresis After Dialysis</i>
			<i>Before</i>	<i>After</i>	
Hepatorenal syndrome ⁹	8 days	111 hrs. 80 L 60 gm.U+	190	58	2 days
13 yrs. Acute Nephrosis ⁹	7 days	4½ hrs. 34 L 45 gm.U+	120	65	1 day
54 yrs. Acute Nephrosis ⁹	5 days oliguria	5 yrs. 60 L 66 gm.U+	150	80	2 days
50 yrs. Sulfa drugs ⁹	4 days	51 L 52 gm.U+	100	49	2 days
23 yrs. HgCl ₂ ⁹	7 days	39 gm.U+	174	69	3 days
31 yrs. Crush syndrome ¹⁵	8 days 150 cc.	5 hrs. 21 L 32 gm.U+	180	100	3 days
52 yrs. Postoperative (myanesis hemolysis) ¹⁵	26 days (output 1 L daily)	41 hrs. 19 L 38 gm.U+	200	120	9 days
26 yrs. Abortion ¹⁵	9 days (output 35 cc. daily)	1.8, 7 hrs. .67 gm. NPN	120 NPN	65 NPN	3 days
40 yrs. Transfusion reaction ¹⁵	8 days	26 hrs. 49.4 gm. NPN	179 NPN	100 NPN	1 day

TABLE IV—TWO MOUNT SINAI HOSPITAL CASES RECOVERED AFTER DIALYSIS IN ARTIFICIAL KIDNEY²⁰

Diagnosis	Anuria	Dialysis	Blood Urea Nitrogen Mg.%		Diuresis After Dialysis
			Before	After	
25 yrs. HgCl ₂	5 days	6 hrs. 50 gm. U+	150	70	7 days
30 yrs. CCl ₄		1st dialysis			
	9 days	6 hrs. 34 gm. U+	108	54	
	15 days	2nd dialysis 6 hrs. 41 gm. U+	85	35	2 days after 2nd dialysis

Alwall has treated five patients, three with acute and chronic nephritis, one with polycystic kidney and one with a carcinomatous obstruction of the ureters. In all patients the urea and other nitrogenous waste products which had accumulated in the blood were reduced considerably. All felt better after the dialysis but they died shortly thereafter from the original disease.

At the Mount Sinai Hospital six patients with anuria have been treated with the Kolff kidney (Fishman *et al*²⁰). Four were in the last stages of uremia and died shortly after the dialysis. The two last patients were in better shape before the treatment started and recovered after dialysis (Table IV).

The first patient was a woman, 25 years of age, who had introduced 2.5 grams of mercury bichloride in tablets into the vagina. She was admitted on the fifth day of the anuria and only then was B.A.L. treatment started. She had extensive necrosis of the mucous membranes of the mouth and vagina. The hemoglobin had gone down to 8.5 grams and the general condition was very poor indeed. The blood serum contained large amounts of urea and other nitrogenous products, the carbon dioxide combining power was 26 volume per cent.

On the night of admission dialysis with the artificial kidney was performed. The injection of 250 mg. of heparin proved to be sufficient to keep the clotting time of the blood between one and four hours during the six hours the dialysis lasted. The dialysis resulted in the removal of 24 grams of urea nitrogen, 6.7 grams of uric acid, 9.7 grams of creatinine and 6.5 grams of protein. At the end of the dialysis the non-protein nitrogen of the blood had diminished from 150 mg. per cent to 70 mg. per cent, the urea nitrogen from 116 mg. per cent to 30 mg. per cent, the uric acid from 14 mg. per cent to 6.9 mg. per cent, the creatinine from 14.1 to 3.7 mg. per cent, the inorganic

phosphorus from 7 to 1.5 mg. per cent. During the dialysis the general condition of the patient improved considerably. Nevertheless, the following days were critical because of severe vomiting and diarrhea. The urea nitrogen rose again notwithstanding a gradual increase of the urinary output. On the seventh day after dialysis the quantity of urine approximated the intake of fluid. However, only when the diuresis increased to several thousand cc. and the urea nitrogen concentration of the urine approached 400 mg. per cent, did the nitrogenous retention products begin to disappear from the blood. During this period a diet high in carbohydrate, high in fat and with extreme limitation of protein was given. The intake of fluid was restricted to about one liter for every 24 hours. On an average daily approximately 4 grams of sodium chloride and 16 grams of sodium bicarbonate were given by mouth, depending upon the chloride content and the carbon dioxide combining power of the serum. Ultimately, the renal function returned to normal.

The second patient was a man of 30 years who for five hours had been exposed to fumes of carbon tetrachloride. Seven days after the intoxication the patient became completely anuric. On the eighth day he was admitted to the Mount Sinai Hospital. He was severely uremic, with high nonprotein nitrogen (170 mg. per cent) and acidosis (carbon dioxide combining power of 28 volume per cent). On the second day after admission the patient was treated with the artificial kidney for six hours. The injection of 250 mg. of heparin resulted in a satisfactory retardation of the clotting. During the dialysis 34 grams of urea, 3.6 grams of uric acid, 12.4 grams of creatinine, 4.1 grams of inorganic phosphorus and 8.3 grams of protein were removed. The blood urea nitrogen came down from 108 mg. per cent to 54 mg. per cent, the uric acid from 11.3 mg. per cent to 8.3 mg. per cent, the inorganic phosphorus from 4.1 mg. per cent to 3.1 mg. per cent. Extreme oliguria persisted and the nitrogenous waste products accumulated again in the blood. Six days after the first dialysis he was treated for the second time with the artificial kidney for six hours. During the dialysis 41 grams of urea, 3 grams of uric acid, 16.7 grams of creatinine, 2.7 grams of inorganic phosphorus and 22 grams of protein were removed. The blood urea nitrogen came down from 85 mg. per cent to 35 mg. per cent, the uric acid from 5.6 mg. per cent to 2.5 mg. per cent, the creatinine from 27.2 mg. per cent to 19.8 mg. per cent, the inorganic phosphorus from 7.5 mg. per cent to 3 mg. per cent. Two days later, diuresis set in which resulted in a gradual recovery.

The clinical course in this case was characterized by freedom from uremic manifestations despite a long period of renal insufficiency and the accumulation of large amounts of urea and other retention products in the serum.

Everytime a patient with anuria and uremia recovers after treatment with the artificial kidney, the question can be raised as to whether this patient would not have recovered spontaneously. This holds true especially for patients who are no longer completely anuric and where oliguria has already replaced the anuria. During the first weeks after diuresis has started, retention of urea and other catabolic products in the blood may still be progressive. As long as the urea concentration in the urine is less than 400 mg. per cent the urea nitrogen and the non-protein nitrogen of the blood continue to increase. It may be advisable to dialyze such an oliguric patient in order to relieve the blood from the excess of waste products, but in such cases the artificial kidney can hardly be considered to have acted as a life-saving device. The difficul-

TABLE V—PERITONEAL DIALYSIS

<i>Animal Experiment</i>			
1923	Putnam	Cats	Intermittent
1923	Ganter	Guinea pigs	Intermittent
1925	Lanzberg & Gnoinski	Guinea pigs	Intermittent
1926	Rosenak & Siwon ²¹	Dogs	Continuous
1927	Heusser & Werder ²²	Dogs	Continuous
1932	Bliss, Kastler & Nadler	Dogs	Intermittent
1932	Von Jeney	Dogs	Continuous
1932	Von Haam & Fine	Rabbits	Intermittent
1946	Abbott & Shea	Dogs	Intermittent
1946	Seligman, Frank & Fine	Dogs	Continuous

ties encountered in the appraisal of such cases are clearly demonstrated by the following patient.

Three days after exposure to carbon tetrachloride a patient developed anuria. After the anuria had lasted for three days, diuresis started. Unfortunately, he then was treated with large amounts of fluid and saline so that when ten days after the intoxication he was admitted to The Mount Sinai Hospital, left heart failure had set in. In the Hospital the daily diuresis gradually increased. On the first day of admission it was only 260 cc., on the sixth day of admission, that is, 16 days after the intoxication, it had risen to 1605 cc. Notwithstanding this apparently satisfactory output, the urea nitrogen of the blood had increased progressively to 212 mg. per cent. Patient was irrational and heart failure still persisted. The outlook seemed hopeless. On the night of the 16th day, the patient would have been dialyzed were it not that the artificial kidney was out of order. In the next days the diuresis increased rapidly and the patient recovered spontaneously. Nine days later the blood urea nitrogen was only 28 mg. per cent.

Summarizing it must be pointed out that no certain conclusion can be reached as to whether dialysis by the artificial kidney is actually a life-saving device. At the same time, in the eleven patients who recovered the artificial kidney seems to have had a favorable influence upon the course of the disease. Thus the circumstantial evidence appears

to be in favor of the opinion that dialysis in the artificial kidney results in temporary improvement which may perhaps make survival possible until restoration of the renal function sets in.

PERITONEAL DIALYSIS

History: As in a real dialyzer substances travel from the peritoneal cavity to the blood and in the reverse direction, with the exception of colloids. Table V shows that the method of peritoneal dialysis has been developed gradually and is based upon a long series of experiments. The first experiments with continuous peritoneal dialysis were done by Rosenak and Siwon.²¹ After intraperitoneal injection of a solution which is similar in ionic concentration and in osmotic pressure to plasma, no change in the composition of either the peritoneal fluid or plasma occurs. Solutions used for peritoneal dialysis should therefore contain not more than 0.6 per cent of sodium chloride (Table VI).

Seligman, Frank and Fine¹⁰ calculated from their dog experiments that if 1.8 to 3 liters of fluid flow through the abdominal cavity per hour, a urea clearance of 12 to 16 cubic centimeters of blood per minute is obtained. Later Kolff and Kop²² found in humans that when the inflow of the dialyzing fluid into the peritoneum is kept at one liter per hour, a urea clearance of eleven centimeters of blood per minute results. These figures agree very satisfactorily. It follows that removal of catabolic products from the blood by peritoneal dialysis is equivalent to 40 to 75 per cent of the clearing capacity of the kidneys.

The amount of urea and nitrogen derivatives which can be removed from the blood of uremic patients by peritoneal dialysis of three days duration varies between 20 and 60 grams. In one case Kolff and Kop even removed 300 grams of urea. During the dialysis the urea content of the dialyzing fluid goes up to about 50 per cent of the urea content of the blood.

Results: Table VII shows the increase of popularity of peritoneal dialysis as a clinical method in this part of the world since the publications of Seligman, Frank and Fine.¹⁰

In 1927 Heusser and Werder²³ reported experiments with intraperitoneal dialysis on dogs. In the same article they mention briefly, in passing, that they also treated three uremic patients with continuous peritoneal dialysis. The results were not favorable evidently, because not enough fluid passed through the peritoneal cavity.

TABLE VI

	Cunningham and Darrow	Frank, Fine and Seligman (Tyrode ¹⁸)	Hartmann	Abbott and Shea "A" solution	Odell and Ferris and Pearson ²⁷ "P" solution	Kolff ²⁸ Artificial Kidney	Kolff and Kop ²² peritoneal dialysis
NaCl Mg. %	650	800	600	610	600	600	600
NaHCO ₃ Mg. %	250	100		220	300	200	200
KCl Mg. %	18	20	40	35	20	40	40
CaCl ₂ Mg. %		10	20	23	10		28
NaH ₂ PO ₄ Mg. %		5		7	5		
MgCl ₂ Mg. %		10		5	10		
Glucose %		1½		1-2	2	1-3	1-3
Natrium-lactate			240				

Different solutions used for peritoneal dialysis

TABLE VII—PERITONEAL DIALYSIS IN HUMANS

	Cases	Survived
1927 Heusser and Werder ²³	3	0
1934 Balasz and Rosenak ²⁴	2	0
1938 Rhoads ²⁵	2	0
1938 Wear, Sisk and Trinkle ²⁶	5	1
1946 Fine, Frank and Seligman ¹⁹	4	1
1946-1948	64	19
Total	80	21

In 1934 together Balázs and Rosenak²⁴ published the first complete observations on continuous peritoneal irrigation in two patients with fatal uremia, due to mercury poisoning. In the first case the dialysis lasted only for thirty minutes during which time the peritoneum was perfused with 12 liters 4.2 per cent glucose solution. Only a few grams of nitrogen were removed. The same holds true in the second case where 19 liters of 0.8 per cent sodium chloride solution were used as dialyzing fluid.

Rhoads²⁵ in 1938 treated two patients with chronic nephritis in the same way. He removed large amounts of urea. The patients reacted favorably but died ultimately from their disease. Wear, Sisk and Trinkle²⁶ in 1938 treated five patients with continuous peritoneal dialysis. One patient who was uremic and had a stone in the urinary bladder survived. In his case peritoneal dialysis with Locke solution resulted in the removal of 16.4 grams of urea. The non-protein nitrogen of the serum came down considerably, the patient could be operated and recovered. Thus previous to the publication of Fine and associates, twelve patients had been treated with peritoneal dialysis of whom one²⁶ recovered. Four patients were treated by Seligman, Frank and Fine.¹⁰ One patient with anuria after sulfathiazole medication recovered. This was probably the first patient where the possibility that peritoneal dialysis had worked as a life-saving device could be considered. Since their article more than 68 patients have been treated of whom nineteen recovered.^{22, 27-37} Twenty-one of the eighty-one cases published were treated by Kolff and Kop with five survivors.²² Table VIII mentions the cause of anuria in the patients who survived. Table IX illustrates that success has been obtained even in cases where the composition of the dialyzing fluid was not optimal.

Comparison between the artificial kidney and peritoneal dialysis shows that both methods have their advantages and disadvantages. Heparinization necessary for treatment with the artificial kidney may cause disagreeable hemorrhages during and after the treatment. This danger is greatly decreased since protamine sulphate has become available. Peritoneal dialysis cannot be used immediately after an abdominal operation or when extensive adhesions or peritonitis are present. The artificial kidney is a complicated apparatus which requires adept handling by an expert team whereas the instruments necessary for peritoneal dialysis are simple.

TABLE VIII—RECOVERY AFTER PERITONEAL DIALYSIS

Transfusion reactions	5
Mercury intoxication	4
Sulfathiazole	2
Anuria due to other causes (hyperemesis, prostatism, etc.)	10

TABLE IX—SOLUTIONS USED FOR PERITONEAL DIALYSIS
IN 19 RECOVERED PATIENTS

Kolff and Kop solution	5
Tyrode solution	6
Hartmann solution	3
A. solution	2
P. solution	1
0.9% NaCl	1
Locke solution	1
1.8% NaCl	1
Different solutions	1

The fact that Kolff and Kop also used the artificial kidney in six of the twenty-one patients whom they treated with peritoneal dialysis shows that the indications for both methods often run parallel (blood urea nitrogen of about 180 mg. per cent, increased potassium content of the serum or marked acidosis). Other investigators start dialysis in patients with mercury poisoning when the anuria exists for three days. Clinical experience has shown that in such cases the outlook is very serious indeed, even if the urea nitrogen content of the blood has not yet reached a level of 180 mg. per cent.

In every patient with uremia due to anuria who recovers after peritoneal dialysis, the possibility that recovery could have been a spontaneous one has to be considered. In addition the dangers and complications of this method should not be underestimated. Peritoneal infection, difficulties in maintaining a satisfactory flow through the peritoneal cavity,³⁸ abdominal colic and meteorism are frequently the reason why a dialysis has to be terminated prematurely.

Nevertheless, in some of the twenty patients who recovered after

peritoneal dialysis the method apparently has had a favorable influence upon the course of the disease.

INTESTINAL IRRIGATION

Introduction: It is true that by irrigation of the intestine, especially of the small intestine, nitrogenous products can be removed from the blood. However, it seems hardly appropriate to designate intestinal irrigation as intestinal dialysis. Intestinal irrigation cannot be identified with dialysis in the artificial kidney or through the peritoneal membrane. If the dialyzing fluid in the artificial kidney or in the peritoneum is isotonic and isoionic with the plasma, then the quantity of fluid and electrolytes in the artificial kidney or in the peritoneal cavity does not, or hardly changes. In contrast, the intestinal wall has specific absorbing qualities and even from an isotonic and isoionic solution large quantities of salts and water are absorbed. The liberal absorption of water and salts from the intestine irrespective of the composition of the irrigation fluid, is a disadvantage in uremic patients with anuria or oliguria, because it easily leads to anasarca and lung edema. Only a relatively small amount of irrigation fluid can be recovered after intestinal irrigation with isotonic fluids, especially when the irrigating fluid runs in slowly. Thus the concentration of the urea present in the fluid recovered from the intestine is high but the total amount of urea removed is only small.

In order to avoid these disadvantages an isotonic solution of 5 per cent magnesium sulphate has been used for intestinal irrigation in animal experiments. As magnesium sulphate is not, or is hardly absorbed from the intestinal lumen, irrigation with this solution will not lead to absorption of excessive amounts of water or salts. In addition, old experiments (Hamburger³⁹) seem to indicate that the resorptive power of the intestinal epithelium is markedly decreased after it has been in contact with magnesium sulphate. However, the question may be raised whether large amounts of magnesium sulphate even in isotonic solution will have an irritating effect upon the intestinal wall. Most investigators have added at least a trace of a magnesium salt to the irrigation fluid.

Irrigation of the Colon: Landsberg and Szenkier¹⁰ in 1930 experimented on the influence of colonic irrigation on the condition of rabbits made uremic by uranium nitrate. They found that after lavage of the colon through an appendicostomy tube about 20 mg. per cent urea nitrogen was present in the irrigation fluid. The blood urea nitro-

TABLE X—COLONIC IRRIGATION

	Irrigation fluid	B.U.N.
Landsberg and Szenkier.....	U.N. 20 mg.%	Unchanged (rabbits)
Kolf: Case 1	U.N. 18 mg.%	60 mg.%
Case 2	U.N. 5 mg.%	190 mg.%
Daugherty, <i>et al.</i>	U.N. 7 mg.%	180 mg.% before 118 mg.% after
Creatinine unchanged. Hyperchloremic acidosis and polyuria developed		
Removed by irrigation 1.66 gm. N.P.N. } " in urine 19.6 mg. N.P.N. } 6 hrs.		

gen of the rabbits, however, did not decrease after colonic irrigation. Pendleton and West⁴¹ who experimented mainly with the removal of urea from the blood by irrigation of the small intestine felt that the colon could also be used for the same purpose.

The evidence available indicates that in patients with uremia, irrigation of the colon does not lead to the removal of significant amounts of urea and other nitrogenous products (Table X). Kolf⁹ performed colonic irrigation through an appendicostomy. In the first patient thin feces leaked through the anus and further lavage had to be given up. The urea nitrogen content in the escaping perfusion fluid was 18 mg. per cent as compared with a blood urea nitrogen of 60 mg. per cent. In the second patient the thick tube placed in the rectum was closed off by the sphincter ani, and in this way loss of the perfusion fluid was prevented. Although the blood urea nitrogen was 190 mg. per cent, the perfusion fluid only contained 5 mg. per cent nitrogen. Daugherty and associates⁴² also perfused the colon in one patient with uremia through an appendicostomy. The perfusion lasted 64 hours. During this period first 35 liters of P-solution (Table VI), later 5½ liters of a P-solution with reduced sodium chloride (480 mg. per cent), and increased NaHCO₃ content (350 mg. per cent) were used. After the irrigation the patient's weight had increased by 6.25 pounds. The serum chloride rose from 92.3 to 118.5 milliequivalent, the carbon dioxide combining power decreased from 22.8 to 15.4 milliequivalent. Thus during the colonic irrigation hyperchloremic acidosis developed and

the experiment had to be stopped because anasarca and lung edema set in. At the same time the amount of nitrogen removed was very small. In 64 hours, 24.5 liters of irrigation fluid could be collected containing in total, 1.66 grams of non-protein nitrogen (7 mg. per cent). The blood urea nitrogen came down from 180 mg. per cent to 112 mg. per cent after irrigation, but the creatinine content of the serum (8-9 mg. per cent) did not change. The decrease of the urea nitrogen content of the blood may have been secondary to the polyuria which set in during colonic irrigation, evidently caused by the absorption of large amounts of fluid from the colon. During the colonic lavage 8.16 liters of urine containing 19.6 grams of non-protein nitrogen were voided. This figure is in sharp contrast to the 1.66 grams removed by the colonic irrigation. The renal elimination of nitrogen even by diseased kidneys exceeds more than ten times the removal of nitrogen compounds by colonic irrigation.

Irrigation of the Small Intestine: Irrigation of the small intestine seems to have given somewhat more encouraging results.

Pendleton and West⁴¹ in 1932 inserted a rubber tube into the middle third of the duodenum and another large tube into the ileum near the ileocecal junction (Table XI). The bowel above and below the two tubes was tied off. Fluids were run in through the proximal tube and left the small bowel through the distal tube.

When normal saline was placed in the small bowel of normal dogs the urea content of the intestinal contents rapidly rose to levels which sometimes even exceeded slightly the blood urea nitrogen. Then nephrectomized dogs were injected intravenously with urea in order to obtain a rapid rise of the urea in the blood. In one dog the urea nitrogen of the blood went up to 265 gram per cent. Five minutes after the introduction of saline into the small bowel, the urea nitrogen of the intestinal content had risen to 25 mg. per cent, after fifteen minutes it was 153 mg. per cent. Two hours after the injection the urea nitrogen of the blood was 290 mg. per cent, of the solution in the intestine 299 mg. per cent. After three hours the blood urea nitrogen had fallen to 245 mg. per cent while the bowel still contained 281 mg. per cent. In order to prevent the absorption of large quantities of water Pendleton and West later used 5 per cent magnesium sulphate solution as irrigation fluid. The urea passed quickly from the blood to the magnesium sulphate solution in the intestine and after a short time the urea of the

TABLE XI—IRRIGATION SMALL INTESTINE IN DOGS

	<i>In Irrigation Fluid</i>	<i>B.U.N. mg.%</i>		<i>Time</i>	<i>Dogs NaCl 9.9%</i>
		<i>Before</i>	<i>After</i>		
Pendleton and West	280-290 mg.% U.N.	299	245	3 hrs.	
Rogers <i>et al.</i>	4.3-5.4 gm.	198	126	6 hrs.	
	N.P.N.	190	112		
		231	145		
Seligman <i>et al.</i>	Loop of 10 feet—10% of maximal renal clearance				

blood and bowel contents were equal. After introduction of the magnesium sulphate solution a constant fluid volume was maintained in the intestine. In these animal experiments the magnesium sulphate did not cause any difficulties from bowel irritation.

Fine, Frank and Seligman¹⁰ performed continuous irrigation of an isolated loop of ileum, but could remove only small amounts of urea. They calculated that continuous perfusion of a loop of small intestine of 10 feet long would be necessary in order to obtain a urea clearance of 7.5 cc. of blood per minute, that is, about 10 per cent of the maximal normal renal clearance.

Rogers, Sellers and Gornall¹³ placed a thin triple bore rubber tube with a small balloon on the tip in the small intestine of dogs (Table XI). They had to manipulate the tube into position through an abdominal incision. Warm physiological saline was introduced above the inflated balloon and withdrawn through another opening of the same tube several feet higher up. Using 12 to 18 liters of perfusion fluid over a period of about six hours, they were able to reduce the non-protein nitrogen of the serum of nephrectomized dogs considerably. In one case the azotemia was lowered from 198 to 126 mg. per cent. In two other cases from 198 to 112 mg. per cent and from 231 to 145 mg. per cent respectively. The rinsing fluid after perfusion contained 4.3 to 5.4 grams of non-protein nitrogen.

The literature mentions the following patients in whom uremic conditions were treated with intestinal irrigation (Table XII). Kolff⁹ irrigated an isolated loop of ileum 40 inches long in a patient with uremia. Each end of the loop was connected with the outside by an

TABLE XII—IRRIGATION SMALL INTESTINE IN UREMIA

	<i>In Irrigation Fluid</i>	<i>B.U.N. mg.%</i>		<i>Time</i>	<i>Irrigation Fluid</i>
		<i>Before</i>	<i>After</i>		
Kolff.....	2.3 gm. U.N.	Unchanged		10 h.	Kolff solution
Daugherty <i>et al.</i>	4 gm. U.N. in 24 h. (10 mg.%)	155	130 150 (creatinine unchanged)	24 h. 48 h.	P-solution
Oppenheimer and Rosenak.....	70 & 110 mg.% U.N.	90 83	83 46	5 h. 18 h.	Modified Tyrode solution
Marquis and Schnell....		330	121 66	12 h. 24 h.	NaCl 0.9% or Glucose 10% or NaCl 0.8% plus NaHCO ₃ 0.1%
	Creatinine unchanged 49			7 d.	

NaCl 0.9%:—Edema and ascites
Glucose 10%:—acidosis

NaCl 0.8% and
NaHCO₃ 0.1%—hypokaliemia

ileostomy. The continuity of the remaining ileum was restored by an end to end anastomosis. Infection, followed by cicatrization of both stomas of the loop, rendered perfusion of the isolated loop difficult and lavage was only occasionally successful. The best result was obtained when eight liters of fluid passed through the loop in the course of ten hours. During this time 2.3 grams of urea nitrogen were removed. When the lavage fluid runs in very slowly the return flow is necessarily very small. Under these circumstances, the urea nitrogen of the irrigation fluid may go up to 100 mg. per cent. If the perfusion rate is kept to one liter per hour, about 200 mg. of urea nitrogen can be removed per hour. There is probably no advantage in letting the fluid run much faster. It follows that if irrigation during 24 hours would have been possible, nearly 5 grams of urea nitrogen could have been removed every day. This, together with a diet of only fats and carbohydrates, might well keep a nephritic patient at least temporarily in balance. However, the difficulties of perfusion of the ileum loop in Kolff's patient were so great that definite conclusions could not be reached. Kolff used as perfusion fluid the same solution as he used for dialysis with the artificial kidney (Table VI).

Other clinicians have tried to irrigate the small intestine by using

Miller-Abbott tubes or comparable instruments. It is evident that nausea and vomiting as regularly seen in uremia must be a great hindrance to the intra-nasal introduction of Miller-Abbott tubes. A return tube, small enough to be passed by oral or nasal route will usually be too thin to collect large amounts of the irrigated fluid. Thus, too much fluid remains in the bowel and leads to diarrhea. Repeatedly an appendicostomy has been performed through which the irrigation fluid could be sucked out by a pump. The capacity of an appendicostomy tube is not sufficient to cope with large amounts of irrigation fluid and Daugherty and associates are even suggesting that a cecostomy be performed for this purpose.

Daugherty⁴² performed intestinal irrigation in a patient with chronic nephritis. The fluid was introduced via a nasal tube which was pushed into the duodenum. At the same time an appendicostomy was performed through which a tube connected with a suction pump was introduced. In this case, also, the suction through the appendicostomy was insufficient and profuse watery stools were produced. During twelve hours of intestinal irrigation 2,750 cc. of fluid were recovered through a rectal tube and only 300 cc. through the appendicostomy tube. The intestinal irrigation was continued for two days at the end of which the patient died. The urea nitrogen of the serum at the beginning of the experiment was 155 mg. per cent, after one day of irrigation it was 130 mg. per cent, and after two days it was again 150 mg. per cent. The creatinine of the serum was high and did not change, the chloride content of the serum rose slightly from subnormal to normal values. The carbon dioxide combining power remained about the same. In 2,010 cc. of fluid recovered from the rectum 10 mg. per cent of urea nitrogen was found.

Oppenheimer and Rosenak⁴⁴ passed a modified Miller-Abbott tube through the nose until it reached the middle part of the small intestine. Over a period of five hours four gallons of a solution containing NaCl 0.669 per cent, KCl 0.004 per cent, CaCl_2 0.013 per cent, Mg. lactate 0.0065 per cent, acid sodium phosphate 0.0005 per cent, sodium bicarbonate 0.15 per cent and glucose 1.5 per cent were introduced. The next day six gallons were given in the course of 18 hours. During this procedure the blood urea nitrogen went down from 90 mg. per cent to 46 mg. per cent. The recovered fluid contained 111 and 70 mg. per cent of non-protein nitrogen. They also experienced difficulty in re-

covering the irrigation solution because too much was absorbed. This may explain the relatively high concentration of the nitrogen content of the fluid recovered. At the same time the patient suffered from diffuse watery diarrhea.

Marquis and Schnell⁴⁵ reported a case where at least the technical part of the intestinal irrigation was efficient. After two days of anuria due to ingestion of cleaning fluid the patient became completely comatose. Non-protein nitrogen had risen to 330 mg. per cent. At this time two Miller-Abbott tubes were placed in the small intestine, one in the third portion of the duodenum and the other in the lower part of the ileum. In twelve hours 22 liters of fluid were run slowly through and the non-protein nitrogen of the serum dropped to 121 mg. per cent, twelve hours later it was 66 mg. per cent. In the fluid recovered the non-protein nitrogen went up to 50 mg. per cent. Intestinal irrigation was continued for seven days. Gradually diuresis set in and the intestinal irrigation was continued on a half-time schedule. Ultimately it was discontinued. In the next forty-eight hours the urea nitrogen of the blood rose rapidly from 49 to 103 mg. per cent, and the intestinal irrigation was reinstituted. On the tenth day of intestinal irrigation the patient suddenly died.

During the first twenty-four hours of irrigation with 42.7 liters of normal saline, six liters of fluid were retained and general anasarca set in. Thereafter, 20 per cent glucose was used instead of saline. The edema, ascites and hyperpnea disappeared, but acidosis set in. Ultimately 0.8 per cent sodium chloride combined with 0.1 per cent sodium bicarbonate was used. The decrease of the urea nitrogen of the blood indicates that in this way large amounts of urea were removed. As in the other cases of intestinal irrigation the creatinine content of the serum remained high and did not change. The cause of death in this case may have been due to the removal of large amounts of potassium during the irrigation. On the day before death there were many extra systoles. The potassium content of the serum was determined but the result was reported after the death of the patient. The potassium content was found to be 4.6 mg. per cent instead of 16-19 mg. per cent and the patient may well have died from ventricular fibrillation.

It seems that this is the only case where intestinal irrigation was performed in an efficient way. This must have been due to the fact that two Miller-Abbott tubes were introduced. It is evident that in nauseated,

uremic patients such a procedure would be impossible. It seems probable that the authors only succeeded because their patient was comatose and did not resist too much against this heroic treatment. Nevertheless, even this patient pulled out both tubes twice and vomited the proximal tube on one occasion.

Summarizing it seems certain that colonic irrigation is useless as far as the treatment of uremia is concerned. It still has not been proved whether intestinal irrigation of the small intestine has a future in the treatment of uremia and anuria. Table XII illustrates that by this method relatively small amounts of urea are removed. It is probably significant that in the two best cases reported the blood urea nitrogen decreased considerably but the creatinine content of the blood did not. Finally no satisfactory method for efficient intestinal irrigation has been devised yet and dangerous, even fatal complications have been caused by changes of the electrolyte content of the blood.

EXSANGUINOTRANSFUSION

It has been known for many years that an uremic animal can be kept alive by exchange transfusion. An artery of the uremic animal is connected with the vein of the donor animal, a vein of the uremic animal with an artery of the donor. Formerly, paraffinated cannulae were used, nowadays heparin is injected. This favorable result is evidently due to the replacement of the blood of the uremic animal by normal blood (Nyiri,⁴⁶ Thalhimer,¹⁴ Thalhimer, Solandt and Best⁴⁷).

The same principle is used in the exsanguinotransfusion where the total mass of the patient's blood is replaced by an equivalent quantity of normal blood. This method has been used rather extensively in newborns suffering from erythroblastosis fetalis and lately by Bessis and Bernard⁴⁸ in adults suffering from leukemia. Very recently at the instigation of Bessis this method has been used to obtain improvement in the condition of uremic patients (Pasteur Vallery-Radot, Milliez and Bessis), and it has been successful in six of seven cases. To illustrate the difficulties connected with the exsanguinotransfusion the case treated by Tzanck and Dausser⁴⁹ may be mentioned (Table XIII). They treated a forty-year old patient who had taken 16 capsules each containing 0.5 grams of *aspidium filicis maris* and 0.05 grams of calomel. The patient, in order to hasten the expulsion of the taenia also took magnesium citrate and sodium bicarbonate. It is well known that it is dangerous

TABLE XIII—INTOXICATION WITH FILIX MAS AND MERCURY TREATED WITH EXSANGUINOTRANSFUSION⁴⁹

Day	Urinary Output in cc.	Blood Urea Nitrogen Mg. %	Blood Withdrawn	Injected
7	150	163	4 L 11 gm. U+	3.25 L blood 1.2 L NaCl 0.9%
8			3.65 L 9.6 gm. U+	2.55 L blood 1.00 L NaCl 0.9%
9	175	150	6 L 15.8 gm. U+	4.2 L blood 1.7 glucose 5%
10		153	5 L 14.87 gm. U+	3.5 L blood 1.5 L glucose 5%
11	280	133	5 L 12. gm. U+	3.5 L blood 1.4 L glucose 5%
12	375	130	5.5 L 12.9 gm. U+	3.8 L blood 1.6 L glucose 5%
14	300	151	6 L 16.26 gm. U+	4.2 L blood 1.8 L glucose 5%
15	675			
16	3,000		6 L 9.9 gm. U+	4.2 L blood 1.8 L glucose 5%
Total.....			41.5 L blood 103.2 gm. U+	29.2 L blood and 12.0 L diluting solution

to take alkaline compounds together with calomel because soluble toxic mercury compounds may be formed. On the seventh day of oliguria the urinary output was down to 150 cc.; the urea nitrogen of the blood up to 163 mg. per cent. Patient was somnolent and showed involuntary muscular contractions. On this day the first exsanguinotransfusion was performed.

Three and one-quarter liters of blood were injected diluted with 1.1 liters of normal saline. The transfusion lasted 19 hours and 11 grams of urea nitrogen were removed with the blood. The next day 3.65 liters of blood containing 9.6 grams of urea were extracted and 2.5 liters of blood diluted with 850 cc. of normal saline injected. The next day another 6 liters of blood containing 15.8 grams of urea were extracted and 4 liters of blood diluted with 1.3 liters of 5 per cent glucose were injected. The blood urea nitrogen remained about 150 mg. per cent. The daily diuresis did not exceed

175 cc. The next day the blood urea nitrogen was 150 mg. per cent, the patient was somnolent and had involuntary muscular contractions. A fourth exsanguinotransfusion was performed. Five liters of blood were withdrawn, containing 14.9 grams of urea which were replaced with the equivalent amount of diluted blood. This operation was repeated on the next two days, 5 liters and 5.5 liters of blood were withdrawn, containing 12 and 12.9 grams of urea respectively. The urea nitrogen of the blood diminished slightly to 132 mg. per cent, the urinary output went up to 280 cc. and 375 cc. per day. Two days later the blood urea nitrogen had increased again to 151 mg. per cent, the daily urinary output did not exceed 300 cc. Another exsanguinotransfusion was performed. With the blood 6.3 grams of urea were withdrawn and 6 liters of diluted blood were injected. Thanks to the injection of 200 mg. of heparin this and the following procedures lasted two to three hours each. Now the output improved to 675 cc. per day. Two days later the eighth and last exsanguinotransfusion of 6 liters was performed. After this operation diuresis set in with a vengeance and amounted to 3 and 4.5 liters per day. The urea concentration of the urine increased gradually. The blood urea nitrogen decreased accordingly and on the twentieth day it was 43 mg. per cent.

During a total of eight exsanguinotransfusions given over ten days, 41.15 liters of blood were withdrawn and 41 liters of fluid were injected, consisting of 29.2 liters of blood and 10.8 liters of saline or glucose. The urea eliminated by the exsanguinotransfusion together with the small amounts of urea eliminated in the urine amounted to 125.9 grams. In this way every day an average of 12.6 grams of urea were removed. This may be the reason why notwithstanding persistent extreme oliguria the blood urea nitrogen instead of increasing, remained at the same level or even diminished slightly.

The advocates of this method emphasize that it has definite advantages over the treatment with the artificial kidney, peritoneal dialysis, and intestinal irrigation (Table XIV). In contrast to the other procedures the exsanguinotransfusion removes all toxic substances whether dialyzable or not, improves the protein, water and electrolyte content of the plasma and does not cause hemolysis.

In addition the French authors are of the opinion that the large quantities of fresh blood injected do not represent a simple substitution treatment. They believe that the blood of the anuric patient, full of toxic retention products, inhibits the functions of different organs. The fresh blood permits a resuscitation of the functions not only of the kidney but also of the other organs as well. Injection of heparin, about 200 mg. per operation, permits shortening of the procedure to two to three hours. On the other hand, the procedure is extremely laborious and quite expensive unless there are many members of the family who are in a position to donate the many liters of blood which are necessary.

TABLE XIV

<i>Replacement Transfusion</i>	<i>Intraperitoneal dialysis</i>
1. Withdraws all toxic products including those which are non-dialyzable (hemoglobin, myohemoglobin).	Withdraws only dialyzable products.
2. Replaces the pathological blood by normal blood and re-establishes the normal equilibrium of the body fluids.	Withdraws not only pathological products but also certain useful dialyzable substances.
3. Incidents not serious; accidents caused by irregular agglutinins prevented by necessary precautions.	Peritonitis frequently noted, either of the plastic type by adhesions or of an infectious type (septicemias due to <i>B. perfringens</i> post abortum).
4. Can be repeated as often as needed.	Usually cannot be prolonged for more than 5 days. Difficult to repeat due to the formation of adhesions.
5. Disadvantages: large quantities of blood, sometimes of a rare type must be available. Heparinization necessary.	

There may however be instances where repeated exsanguinotransfusions will enable the anuric patient to survive until spontaneous diuresis sets in.

SUMMARY

The treatment of anuria in acute glomerulonephritis and in lower nephron nephrosis is of great practical importance. Acute glomerulonephritis has a tendency to heal spontaneously and in lower nephron nephrosis regeneration of the tubules always starts after ten days have elapsed. Therefore, everything must be done in order to assure survival of the patient for ten or fourteen days after the anuria has started.

The outstanding measure in the treatment of acute anuria consists of reduction of intake of fluids, electrolytes and proteins. In general, the daily fluid intake should not exceed 800 cc. which is sufficient to compensate for the loss of water via the respiratory tract and the skin. In case water is lost by diarrhea or vomiting the fluid intake should be increased. A diet of 800 cc. of fruit juice can be used at least for a

short time. It may be advisable to increase the caloric intake by ingestion of fat and carbohydrate. During hunger considerable amounts of protein are broken down which give rise to the formation of extra urea and other nitrogenous metabolites. For this reason, Borst has advocated a diet consisting of 200 grams of butter and 200 grams of sugar. This diet might well be helpful were it not that for most of the patients the mixture is highly unpalatable. In nearly all cases of anuria intravenous injections of large quantities of fluids and salts are contraindicated. In hypochloremia sodium chloride should be given, in acidosis bicarbonate.

It seems that in most cases of acute anuria these measures will be sufficient to keep the patient alive. Occasionally more drastic measures may be necessary. The latter is often the case in patients with anuria who have been treated with large amounts of fluid and salts. Under these circumstances, the artificial kidney, peritoneal dialysis, intestinal irrigation and exsanguinotransfusion have been used, occasionally with success. All these drastic methods have their advantages and disadvantages and should only be employed if strict indications exist.

At the time of this writing eleven uremic patients have recovered after use of the artificial kidney, twenty-one after peritoneal dialysis. No method is available which permits a satisfactory intestinal irrigation and prevents dangerous changes in the electrolyte content of the blood.

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THE PLACE OF ELECTROLYTE STUDIES IN SURGICAL PATIENTS*

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DURING the past generation surgery has made rapid strides as a result of concentrated attention to the problems of abnormal physiology in patients with surgical diseases. Better understanding of the control of shock, more adequate attention to water and electrolyte balance, and improved anesthesia have been more important than the concurrent advances in surgical technique in giving the surgeon relatively safe access to the contents of the thorax and the brain, the last two anatomical frontiers to be attacked in the evolution of modern surgery. As a result of this shift in emphasis, the surgeon is now called upon as never before to master the practical applications in surgical therapy of fundamental biochemical and physiological methods, particularly if he is unwilling, as are most well-trained surgeons, to turn over to his medical colleagues the nonoperative aspects of surgical care. The surgeon who is willing to relinquish his responsibility for pre- and postoperative care of his patients is in danger of becoming nothing more than a technician and merits no place in the company of scientific medicine. It must be realized that few surgeons are likely to possess the fundamental training in biochemistry and physiology to bring forward new contributions in this field of research. However, it is entirely appropriate and, in fact, essential that surgeons assume the responsibility for applying to their clinical problems the knowledge which has been gained in the pre-clinical laboratories and the parallel research efforts of their medical colleagues. The topic of the present symposium provides a particularly apt illustration of this thesis. Surgeons must share to a large extent the indebtedness which all fields of medicine owe to Folin, Gamble, Peters, Van Slyke, Darrow, and all of their disciples. The work of these individuals laid the foundation for our present understanding of the prob-

* Read at the Stated Meeting of The New York Academy of Medicine, December 2, 1948. From the Surgical Metabolism Unit and the Surgical Service of the Presbyterian Hospital, New York, and the Department of Surgery, Columbia University. The Surgical Metabolism Unit is financed in large part by a grant-in-aid from the Research Grants Division of the U. S. Public Health Service.

lems of fluid and electrolyte balance and no discussion of this subject could be complete without frequent references to their work. However, many of the data which they have recorded, and many of the interpretations based upon these data, are concerned particularly with diseases more frequently encountered by the internist or pediatrician than by the surgeon, and in order to develop the rules of management of conditions of a peculiarly surgical nature, it has been necessary that some surgeons should themselves participate in studies in this general field. Significant contributions in this field have been made by a number of surgeons, including Coller and Maddock, Moore, Moyer, Evans, and Abbott, all of whom are still carrying on active work.

Certain general differences could be pointed out between the problems encountered in surgery and those encountered in the fields of internal medicine and pediatrics. In the first place, the surgeon is more frequently confronted with rapid external losses of body fluids and the resulting intercompartmental shifts between circulating blood, extracellular space, and intracellular fluid compartments. Although most surgical patients enter the hospital with fairly normal kidney function, adequate at least for the prevention of shifts in the hydrogen ion concentration of the blood such as might occur in ordinary degrees of dehydration, the surgical patient is subject to transient disturbances in renal function due to trauma and anesthesia. Very possibly the largest number of problems for the surgeon derive from his dependence upon parenteral fluid therapy at some time during the course of management of every patient undergoing a major operative procedure. A not insignificant proportion of his difficulty in this area may in fact be a *result* of the fluid replacement therapy which he employs, particularly if a selection of fluid has not been based on adequate knowledge of the nature of the existing imbalance. The surgeon must constantly be concerned with the effects of trauma and of operative procedures and anesthesia upon renal function and must recognize that the consequences of over-administration of salt and water during periods of renal dysfunction are just as dangerous as the state of dehydration itself. Edema of the soft tissues and especially of the bowel and the lung is notoriously productive of difficulties for the surgeon, and in the final analysis may account for a significant proportion of postoperative deaths. In recently reviewing a series of case histories of patients dying after radical surgical procedures on the pancreas and duodenum, we

have been impressed with the large number who displayed evidences of improper management in respect to salt and water metabolism. Furthermore, during the past two years, with better attention being given to the avoidance of excessive salt and water replacement, we have been gratified to observe a sharp reduction in the operative mortality from these procedures. We may say without hesitation that the surgeon who is ambitious to maintain his mortality at an irreducible minimum must be just as much concerned with the necessity for physiological fluid replacement therapy as with the technical details of the surgical procedure itself.

The clinical problems of electrolyte balance in surgery fall into three main categories; first, the pre-operative correction of dehydration and electrolyte losses due to the patient's disease. In this category are pyloric stenosis, intestinal obstruction, peritonitis, pancreatitis, and severe burns. Second, the prevention and treatment of imbalance due to the operative procedure and its immediate sequelae. As examples of this, one might cite the ileostomy, the biliary or pancreatic fistula, and the employment of tube drainage of any portion of the intestinal tract. Finally, there is the group of problems mentioned above which derive from improper fluid replacement therapy. The significance of problems in this last category has only recently begun to be appreciated and will receive special emphasis in this discussion.

During the past eighteen months we have maintained on our surgical service a segregated five-bed metabolism ward which is adequately staffed with nurses and technicians so as to permit complete nitrogen and electrolyte balance studies directed toward the solution of some of the major problems in pre- and postoperative care. The original data presented in this paper are a product of the combined efforts of the team of workers assigned to this unit. One of us (H.T.R.) has been particularly concerned with the application to surgical problems of recent knowledge as to the significance of sodium and potassium shifts following periods of dehydration. This work has been made possible by the availability of an accurate flame photometer^{1,2} for direct measurement of sodium and potassium in body fluids, and the work here reported would not have been possible without access to this instrument. The time will undoubtedly come when this instrument will be an indispensable item of equipment in every clinical laboratory. Many of the previous errors in the assessment of the patient's electrolyte status have

been due to almost exclusive reliance upon measurements of chloride and bicarbonate concentrations. Even application of the formulas for indirect calculations of the total base are subject to substantial errors and at the same time fail to give any representation as to the absolute amounts of sodium and potassium in extracellular fluid. Obtained primarily as a research instrument, the flame photometer has now become so essential to the day-to-day management of our regular patients that it has been necessary to install a second instrument for routine laboratory use.

In presenting this subject no apologies are offered for employing the terminology which has been widely popularized by Gamble and other investigators cited above.³ In this terminology the concentrations of the various electrolytes are expressed in terms of milliequivalents per liter rather than in terms of milligrams per 100 cc. of fluid. A very brief discussion of the chemical background for this terminology may not be amiss before proceeding with this discussion. Turning back our none-too-facile memories to the college course in inorganic chemistry we may recall that a molar solution is one comprising the molecular weight of a compound in a liter of water. A milliequivalent of an ion is $1/1000$ of its atomic weight, so that a milliequivalent of the positively charged sodium ion is 23 milligrams. This combines in a liter with a similarly calculated figure for the negative chloride ion, which is 35.5 mgms. to make a total of 58.5 mgms. of NaCl, or a millimolar solution. In discussing concentrations of the various electrolytes, their relationship, or equivalence to one another, is of paramount importance because in the plasma of a normal individual, the sum of the positively charged ions bears a constant and approximately equal relationship to the sum of the negatively charged ions. Variations in this relationship can occur only in conditions of uncompensated acidosis or alkalosis. When chloride ions are lost by vomiting hydrochloric acid, the deficiency of chloride in the extracellular fluid is met by an increase in HCO_3 ions to exactly the same number. Transposition of concentrations as milligrams per cent. to milliequivalents per liter may be made by the employment of formulae derived for each electrolyte from its atomic weight and valence and in making the transition from one system to another, it may frequently be necessary to apply such calculations. It is realized that the use of this terminology has not yet become wide-spread among surgeons, but application of newer knowledge in this field makes it

imperative that surgeons start thinking in these terms. Relations of ions in equilibrium with one another is fundamental to intelligent management of electrolyte studies, and it is impossible to move about in this field of knowledge without the use of modern tools of terminology. The time has come when editors of surgical publications and books should require the expression of electrolyte values in the terms of milliequivalents and millimoles per liter. The change would be no more complicated than that which has been successfully accomplished in transferring from the apothecary's system to the metric system in gravimetric and volumetric expressions.

There is no problem in surgery in which electrolyte studies are more essential than that of the dehydrated patient. However, when a patient comes in with dehydration due to prolonged vomiting, diarrhea, a severe burn, or water deprivation from any cause, the first step is necessarily to establish the diagnosis, but correction of the dehydration should not be delayed while diagnostic studies are being carried out. It is especially important to deal with dehydration promptly if it seems probable that an operative procedure will be required to correct the patient's disease, because dehydrated individuals are notoriously poor-risk subjects and are extremely vulnerable to anesthesia, blood loss, and shock. The dehydrated patient has a reduced blood volume, and a reduced interstitial fluid reserve together with an increased viscosity of the blood, so that the volume flow of blood through the tissues and vital organs is already compromised, and if one adds to this the consequences of anesthesia, transient hypotension, and further reduction in blood volume, the outcome is costly. However, the type of fluid replacement needed and the amount of fluid required will vary significantly according to the degree of dehydration and the source of the water loss. Figure 1, taken from an article of Dr. William Abbott,⁴ shows diagrammatically the volumes of fluid normally available for external loss at different levels of the gastro-intestinal tract. However, the composition of gastro-intestinal secretions varies at the different levels of the tract, and it makes a big difference whether the dehydration is due to pyloric obstruction, when acid gastric secretions are predominant in the fluid-loss, or whether the lesion is a low intestinal obstruction, where the predominant portion of lost fluid is the alkaline secretion of the small bowel. Also the relative amounts of sodium, potassium, chloride, and bicarbonate lost will vary according to the

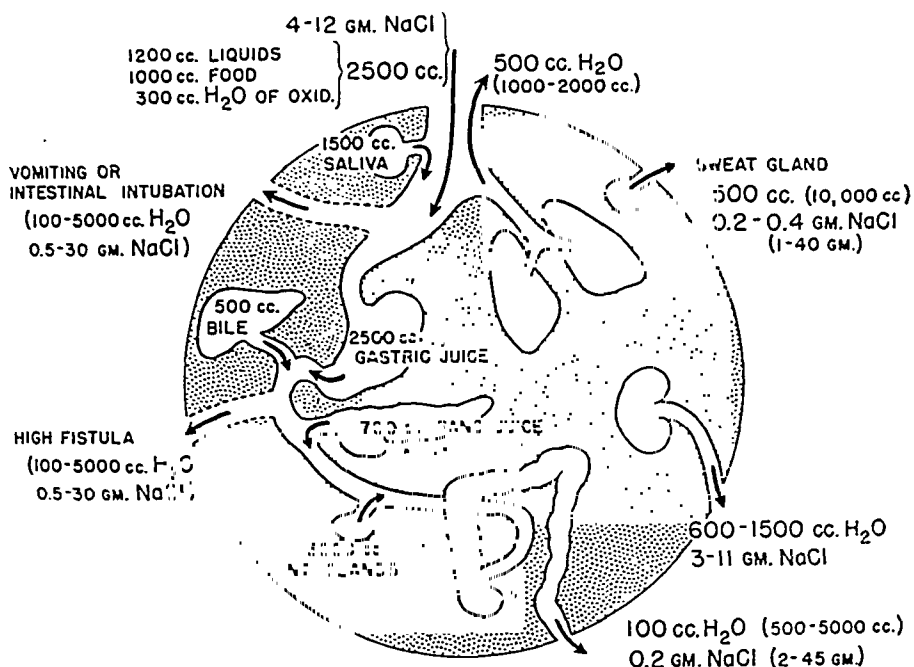


Fig. 1—Quantitative aspects of fluid and salt exchange in health and disease. (Abnormal losses indicated in parenthesis) From Abbott, W. E., *Am. J. M. Sc.*, 211:232, Feb. 1946.*

route of the loss. Table I depicts the composition of fluids withdrawn at different levels of the gastro-intestinal tract. The average values as we have found them are shown together with the extreme range of values which we have encountered in the course of an eighteen-month study of surgical patients. One must guard against assignment of absolute significance to any of these figures because a given lesion rarely drains fluid exclusively from one segment of the gastro-intestinal tract; for example, in an obstructing lesion of the upper jejunum, the vomitus will contain considerable amounts of succus entericus, bile, and pancreatic juice, along with gastric juice. It therefore becomes essential in proper clinical management of such patients to determine the actual concentrations of electrolytes both in the plasma and in the vomitus or other drainage fluid and in the urine as well. Still further information may be obtained through the hematocrit reading, through measurement of the hourly volume flow of urine, and through determination of the plasma volume by the Evans blue-dye technique. The latter determination will be of less value as an absolute depiction of the

TABLE 1A—G.I. TRACT LOSSES M.Eq. PER LITER

	<i>Na</i>	<i>K</i>	<i>Cl</i>
GASTRIC	60.4	9.2	84.0
(Fasting)	9-116	0.5-32.5	7.8-154.5
SMALL BOWEL	111.3	4.6	104.2
(MA Suction)	82.-147.9	2.3-8.0	43-137
ILEOSTOMY	129.4	11.2	116.2
(Recent)	105.4-143.7	5.9-29.3	90-136.4
ILEOSTOMY	46	3.0	21.4
(Adapted)			
CAECOSTOMY	52.5	7.9	42.5
FORMED STOOL	<10	<10	<15

Electrolyte composition of gastro-intestinal fluids. (Upper figure indicates average; lower figure indicates range of observed values.)

TABLE 1B—BILE AND PANCREATIC FISTULAE

	<i>Na</i>	<i>K</i>	<i>Cl</i>
BILE	148.9	4.98	100.6
	131-164	2.6-12	89-117.6
PANCREAS	141.1	4.6	76.6
	113-153	2.6-7.4	54.1-95.2
URINE Normal	40-90	20-60	40-120
Path.	0.5-312	5-166	5-210
TRANSUDATES	130-145	2.5-5.0	90-110

(Upper figure indicates average; lower figure indicates range of observed values.)

degree of reduction in plasma volume than as a baseline upon which to evaluate the adequacy of subsequent rehydration. Also the determination of the total red cell mass as calculated from hematocrit and plasma volume is of considerable value in determining the volume of blood transfusion which should be administered in conjunction with efforts at rehydration. Performance of these biochemical and physiological tests imposes a severe strain on the professional and technical staff of any hospital, but they have become an integral part of surgical management and success in dealing with severe problems of electrolyte imbalance in surgical patients cannot be attained simply by guess-work.

However, there are a few simple principles the observance of which will keep to a minimum the volume of laboratory work required and, more important, will help to keep the surgeon and his patient out of trouble. The balance of this paper will be devoted to emphasis of such points.

1. *Changes in the weight of the patient from day to day are a very useful index of over-all changes in hydration.* Although every effort should be made to measure and record accurately on the hospital chart the total volumes of both intake and output of everything which enters into daily fluid balance, there are often inaccuracies in such measurements. The total insensible loss and loss through perspiration can only be estimated very crudely, and drainage fluids and urine are frequently lost on dressings and bed clothes. The practice of early ambulation makes it possible to record daily patient weights even during the immediate postoperative period. A set of scales with a limit of accuracy of $\frac{1}{2}$ pound is sufficient to obtain the relatively crude appraisal which is all one seeks by this method. In the case of a dehydrated patient it is possible to trace a successful effort at rehydration by progressive weight gain—which in a critical situation might be as much as 3 or 4 kilograms in 24 hours. On the other hand, the patient whose fluid regimen requires alteration because of the development of edema should undergo progressive weight loss if the new regimen has been well designed. Sudden changes in weight must always be accounted for, and unless other obvious causes exist, diurnal variations in excess of one half a kilogram are almost certainly attributable to loss or retention of body water. Attention then turns immediately toward meeting any pathological losses or gains by supplying more or less of whatever type of fluid is concerned.

2. *Every effort should be made to administer fluids by mouth in preference to parenteral routes* whenever the patient's disorder does not contraindicate use of the gastro-intestinal tract. The patient's actual needs for a substance such as salt are likely to be met more accurately by the dictates of his taste for salt than by the calculations of even the most solicitous surgeon, especially if accurate laboratory data are not continuously at hand. Furthermore, there is much less danger of having to meet the consequences of over-treatment if advantage is taken of the "intelligence" of the normally functioning gastro-intestinal tract. When we give sodium chloride solution as the sole source of electro-

lytes, we are failing to provide the significant amounts of potassium, magnesium, calcium, and other electrolytes present in natural foods, and, as will shortly be seen, knowledge is only beginning to catch up with the role of these inorganic ions in metabolism.

3. *Sodium chloride is a potentially dangerous drug, which is frequently indispensable in preserving life, and should be used with respect on both counts.* The normal intake of sodium chloride is generally given as about 2 to 4 grams per day and is approximately the amount excreted daily by the kidneys. This would be equivalent to 250 to 500 cc. of the usual so-called "normal saline" solution. Only under severe conditions of exposure to heat, such as might be encountered in a South African diamond mine, would the physiological requirement of salt for a healthy individual rise to equal the amounts which are often given to surgical patients in 2 or 3 liters of saline solution. Where there is an inability of the kidneys to retain sodium, as in Addison's disease, or where there is an extensive external loss of body fluids which contain sodium, the requirements of NaCl replacement are necessarily increased correspondingly and might even equal the quantities cited.

Specifications of proper requirements of sodium chloride for surgical patients have followed several swings of the pendulum between the extremes of inadequate and excessive salt therapy. However, much of the difficulty which surgeons have encountered has been due to over-reliance on sodium chloride alone in meeting electrolyte deficits. In 1938 Coller and his associates^{5,6} proposed that hypochloremic patients should be given 0.5 gm. of salt per kilogram of body weight for each 100 mgms. that the plasma chloride level needs to be raised to reach the level of 560 mgms. per cent. Application of this rule might call for the administration of as much as 70 gms. of sodium chloride to a large individual who had a reduction of plasma chloride to a level of 360 mgms. per cent. The authors recognized that the need for sodium might not be identical with the need for chloride but stated that the normal kidney was perfectly capable of excreting sodium chloride given in excess of that actually required and that therefore it was desirable to err on the side of too much rather than of too little. However, in 1944 Coller⁷ and his associates published an article on postoperative salt intolerance in which they retracted this clinical rule for salt administration and called attention to the inability of the kidney to excrete sodium chloride during the immediate postoperative

period. They reported a number of cases in which the application of their previously enunciated rule had resulted in serious over-hydration. Coller's new recommendation was that no saline solution of any kind be given during the day of operation and during the subsequent two postoperative days. It was further recommended that if a significant loss of extracellular fluid occurred during this three-day period, it should be replaced with 0.5 per cent sodium chloride solution containing 5 per cent glucose. It was his impression that at least 48 hours were required for the recovery of the kidney from the effects of the operative procedure and that during this interval great care should be exercised in the administration of salt. Administration of sodium chloride above that so required seemed prone to predispose to atelectasis, pulmonary edema, and intestinal dysfunction. Attention was called to the importance of careful observation of the physiological response of the dehydrated patient to test doses of salt solution rather than to reliance exclusively on laboratory determinations of the various electrolytes and other plasma constituents. Further emphasis on the significance of postoperative salt retention was supplied by Van Slyke and his colleagues⁸ who pointed out that significant changes in renal function took place following periods of reduced renal blood flow such as might occur during the course of any major surgical procedure. Numerous students of the physiological mechanisms of cardiac failure have emphasized the effect of altered renal blood flow on salt retention and have even gone so far as to suggest that the edema of cardiac failure is due to renal dysfunction rather than to simple dynamic considerations, as had been previously assumed. Borst⁹ suggests that salt retention by the kidney may be a protective mechanism designed to assist in the maintenance of plasma volume in shock and hemorrhage or in any situation in which cardiac output is decreased, a view similar to that originally held by Starling. Our own observations have confirmed the presence of marked impairment of renal blood flow during operative procedures and the subsequent tendency toward transient retention of sodium. One recent patient of ours excreted only traces of sodium for a period of 11 days during which the volume output of water and of chloride ion was approximately normal. The plasma sodium level was kept within normal limits only by rigidly excluding all sodium chloride from her fluid regimen. This case illustrates an important limitation of the Fantus test for urine chloride, as recently

TABLE II—COMPOSITION OF PARENTERAL FLUIDS
M.Eq. Per Liter

	Na	K	Cl	Effective HCO ₃
0.85% NaCl	146	0	146	0
.9 % NaCl	154	0	154	0
110 Na+30 K	110	30	140	0
1/6M Na Lactate	166	0	0	166
NH ₄ Cl*	0	0	100	0
Dextrose+KCl**	0	30	30	0
Darrow's Solution	120	35	105	50
Hartman's Solution***	136	5.3	112	33
Dextrose in Water	0	0	0	0
Amigen	34	34	..
NORMAL Plasma	140.8	4.28	103	27.6

* 0.5% NH₄Cl+5% Dext.

** 0.223% KCl+5% Dext.

*** 3.6 meq/1Ca++

Electrolyte content of certain parenteral fluids compared with that of normal plasma.

repopularized by Van Slyke and Evans.¹⁰ It is important to call attention to the fact that the kidney may retain sodium and yet excrete chloride in nearly normal amounts, so that the patient's need for sodium may be quantitatively quite different from his need for chloride ion. The results of a test for chloride in the urine may not reflect the condition of sodium balance. Our choice of fluids for electrolyte replacement must therefore be sufficiently flexible to separate these two requirements as necessary in special circumstances. Except when confronted with the problem of correcting or preventing an obvious deficit in body water, a patient should not be given more than his normal 2 to 4 gms. of salt a day or 250 to 500 cc. of saline. Additional requirements of fluid should be met with 5 per cent dextrose in water and additional amounts of salt should be given only upon clearcut indications therefor.

Electrolyte losses from the different levels of the gastro-intestinal tract may be compensated by the administration of fluids better designed than plain sodium chloride solution to meet the deficiencies likely to occur. In Table I is shown how the electrolyte composition of the various gastro-intestinal secretions varies in respect to sodium.

TABLE III—PARENTERAL FLUID REPLACEMENT

	<i>Dext./W</i>	<i>Dext./Sal</i>	<i>M/6Na Lact.</i>
GASTRIC	33%	67%	..
SMALL INT.	20%	70%	10%
ILEOSTOMY	10%	75%	15%
BILIARY	67%	33%
PANCREATIC	50%	50%

Above solutions employed for volume-for-volume replacement of calculated losses. Basal intake should be 1500-2500 cc. with not more than 500 cc. saline.

Formulae which approximate average requirements in volume for volume replacement of gastro-intestinal fluid losses.

Table II shows by contrast the composition of some of the fluids which are available from our own Solution Room. Of these, only Hartman's solution approximates the electrolyte composition of extracellular fluid (plasma). Since it is convenient to replace the volume of fluid lost with a similar volume of replacement solution, it is suggested that the formulae indicated in Table III be employed. All three solutions are readily available in any hospital. When compensating for losses from the stomach on a volume-for-volume basis, it is wise to dilute "normal" saline solution with dextrose in water. When the drainage is from the small bowel such a mixture contains too much chloride, and a small part of 1/6 molar sodium lactate is added. The proportions of lactate increase progressively in the cases of ileostomy drainage, biliary and pancreatic fistulae, respectively. Since the ratio of sodium to chloride loss in pancreatic fistulae is approximately two to one, the appropriate mixture for the latter is equal parts of sodium chloride and sodium lactate. If these mixtures are given in amounts equal to volume of loss and the basal fluid intake is provided as indicated on the table, it is possible to anticipate and avoid some of the most troublesome sequelae of dehydration and over-hydration.

An especial word of caution is needed in regard to salt therapy in patients with low plasma protein levels. The tendency of the hypoproteinemic individual to hold extra water in the extracellular fluid is particularly aggravated in the presence of normal or high levels of plasma sodium. Although hypoproteinemic edema can be partially

combatted by simply withholding salt and permitting the sodium level to fall, the ideal treatment is to administer a high protein diet, and to meet the immediate protein deficit with transfusions of blood, plasma, or albumin. Otherwise, correction of the edema is gained at the expense of a reduced circulating blood volume which is in itself a serious handicap to the patient. It is in the hypoproteinemic patients that improper salt therapy is most likely to result in severe gastro-intestinal and pulmonary edema with marked dysfunction of both systems. Rhoads and his colleagues¹¹ at the Memorial Hospital encountered intractable hypochloremia in hypoproteinemic subjects and were able to correct this hypochloremia with sodium chloride until steps had been taken to restore the plasma protein level to normal. The question may now be raised as to whether these workers were dealing with simple chloride deficits or whether they were in fact confronted with associated potassium deficiencies, a syndrome which we now suspect may be frequently encountered in surgery.

4. *Severe dehydration is associated with loss of intracellular potassium and the patient cannot be restored to health until this potassium deficit is corrected.* Several years ago Darrow¹² called attention to the potassium deficits existing in infants after severe diarrhea and demonstrated that rehydration of these infants must be accomplished with fluids containing potassium as well as sodium. Very substantial reduction in mortality occurred when a combined electrolyte solution was administered in comparison with the mortality rate in patients treated with sodium chloride alone. When the flame photometer became available to us eighteen months ago, we commenced a study of the implications of Darrow's work in surgical patients with results which have been of considerable interest to us. According to Darrow's balance studies, there is a considerable loss of intracellular potassium consequent to the withdrawal of intracellular water in patients whose dehydration has gone beyond simple depletion of extracellular fluid. If sodium chloride solution is then given in amounts sufficient to rehydrate the individual, sodium moves into the cell to replace the lost intracellular potassium. This tends to produce intracellular edema and probable interference with many of the normal metabolic functions of the cell. However, the intracellular sodium can in turn be displaced and returned to its normal extracellular position if sufficient amounts of potassium are given before irreversible changes have occurred. In surgical patients

who are sometimes dependent for many days on parenteral fluids, a potassium deficiency can apparently occur even without the appearance at any time of marked dehydration. This is due to the fact that excretion of potassium by the kidneys goes on at a fairly regular rate of 10 to 20 milliequivalents per liter even in the absence of any potassium intake, the source being entirely endogenous. When the patient's balance requirements of calories and proteins are not being met, as is usually the case in surgical patients, a portion of this potassium loss reflects the nitrogen losses due to tissue catabolism. Furthermore, potassium is present in significant amounts in gastro-intestinal secretions and is especially high in pancreatic juice and bile. Therefore, if a draining fistula is present or if the patient is on gastro-intestinal intubation drainage, such additional losses of potassium will be added to those in the urine. A normal diet would ordinarily contain more than enough potassium to offset such losses. However, the patient who continues to be dependent on parenteral fluids for several days will tend to build up a cumulative potassium deficit equal to many times the normal potassium content of extracellular fluid, a total of only about 50 milliequivalents.

Although the clinical picture of potassium deficiency cannot yet be clearly defined, these patients are usually markedly asthenic and listless and in extreme cases will show myasthenia similar to that occurring in familial periodic paralysis, another potassium deficiency syndrome. Many of these patients give evidence of intestinal and gastric atony, and they are unable to eat adequate amounts of food. Blood chloride levels are normal or low, blood sodium levels are normal or high, the bicarbonate concentrations vary reciprocally with the chloride but are usually high in spite of the co-existence of an acid urine.¹³ We now recognize that many patients who formerly did badly after major operative procedures, and who eventually succumbed, were probably suffering from this basic disorder in metabolism. Fortunately, the response of patients with potassium deficiency to adequate potassium therapy is prompt and frequently dramatic. Immediately after commencement of replacement therapy with a solution containing 30 milliequivalents per liter of potassium chloride, the patient displays an improvement in strength and appetite and usually within three to four days there is a marked diuresis with the excretion of a considerable quantity of sodium, presumably that which had become displaced from

its unphysiological intracellular depot. We have seen several patients become transformed within five to seven days and restored to full health after having previously been in a condition where recovery was despaired of. Caution must always be exercised in administering potassium-containing solutions because of the dangerous consequences of inducing an increase in plasma potassium to levels as high as 9 or 10 milliequivalents per liter, when heart block may occur. However, we have not observed such consequences in the patients we have studied, even though we have given as much as 120 milliequivalents of potassium, or 9 grams, within a twenty-four hour period to patients in whom a serious demonstrated deficiency existed. The specific contraindications of intensive potassium therapy are in those states where blood potassium levels are already high—namely, acute dehydration, severe burns in acute phase, intestinal obstruction, severe renal insufficiency, and during the first twenty-four hours after a severely traumatizing operative procedure. In these conditions the administration of potassium becomes safer after steps toward rehydration have become effectively under way. It is possible that the inclusion of a small amount of potassium, say 5 milliequivalents per liter, or .04 per cent, in all parenteral fluids might be the best means of preventing the development of such severe deficiencies as, once developed, would require therapy with more concentrated potassium solutions. Certainly no danger would exist from giving potassium in such amounts even to patients who did not actually need this ion.

Although much work remains to be done in correlating changes in plasma potassium with changes in potassium content of red cells and muscle tissue, we can now express confidence that the ability to recognize and to deal effectively with this syndrome represents a substantial improvement in the postoperative care of surgical patients.

SUMMARY

The management of problems of water and electrolyte balance is of major importance in surgery because of the numerous instances of dehydration with which the surgeon must deal, and because of the frequent necessity to rely on parenteral fluid therapy for fairly long periods. In meeting these problems the surgeon should be conversant with modern terminology on matters of water exchange and ion equivalents and must receive the benefit of adequate laboratory assis-

tance in following losses and gains of these metabolites. Special considerations of importance are: 1) the usefulness of studying day-to-day changes in weight; 2) the importance of employing natural routes of feeding whenever possible in preference to parenteral routes; 3) the dangers inherent in excessive therapy with sodium chloride, particularly during periods of postoperative and post-traumatic renal dysfunction; 4) the syndrome of potassium deficiency is likely to occur in patients who are given excessive sodium during treatment or prevention of severe dehydration, and in patients carried exclusively on potassium-free fluids for several days.

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SECTION ON MICROBIOLOGY

NOVEMBER 17, 1948

- I. EXECUTIVE SESSION
Reading of the Minutes
- II. SCIENTIFIC SESSION
- a. The Rh factor—general significance and methods of study
Philip Levine
Ortho Research Foundation
 - b. Recent views on the genetics of the Rh-Hr blood system
Herluf H. Strandkov
(by invitation)
University of Chicago
 - c. Medicolegal aspects of the Rh-Hr blood types
Alexander S. Wiener
Office of the Chief Medical Examiner of New York City
 - d. The Rh factor—appraisal of clinical aspects
Peter Vogel
The Mount Sinai Hospital and Department of Health, New York City

The Rh Factor
General Significance and Methods of Study

PHILIP LEVINE

The Rh factor is important clinically because of its capacity to induce isoimmunization when Rh positive blood is administered to Rh negative individuals, either by transfusions,¹ intramuscular injections, or by fetal blood across the placenta.² It has now become a routine procedure to carry out Rh tests on all prospective donors, candidates for transfusion and pregnant women for the prevention of isoimmunization by transfusion and for the diagnosis of hemolytic disease of the fetus and newborn.

The Rh-Hr Factors: The complexity of the Rh factor was noted very early in the course of the initial studies on the path of hemolytic disease of the fetus and newborn.² It is now established that the blood of an Rh negative individual is not devoid of antigenic properties, but it has an agglutinable property known as Hr.³ At least three Rh factors are now recognized, each of which is serologically and genetically associated with corresponding Hr factors.⁴

The incidence of positive and negative reactions with each of the three sets of Rh-Hr factors are given in Table I, along with

other pertinent data.

As first shown by Levine, anti-C and anti-c give three types of reactions; a type of blood failing to react with both anti-C and anti-c does not exist. As anticipated by Fisher, the same relationship holds for both the D-d and E-e systems, and is in striking contrast to the scheme of the four blood groups. It is because of the analogy to the serological and genetic behavior of the M and N factors that the letters in "Rh" were reversed to yield the term "Hr." Accordingly, the three types of bloods correspond to the three genotypes and the blood containing both the Rh and its genetically related Hr factor is heterozygous, while the other two types are homozygous (see Table II).

In each of the three sets, the difference between the positive reaction for the one (Rh or Hr) and the negative for the other (Hr or Rh) gives the incidence of the type which is heterozygous for both. Thus, in the case of the D-d factors, $85 - 37$ or $63 - 15 = 48$ per cent.

The incidence of the three types and of

TABLE I—THE THREE Rh-Hr SERA

Incidence of Reactions (%), Incompatible Matings (%) and Antibodies Produced

	+	—	Incompatible Matings (+ % —)	Antibodies
Anti-D (anti-Rh ₀)	85	15	13	Frequent
Anti-d (anti-Hr ₀)	63	37	23	Very rare
Anti-C (anti-rh')	73	27	20	Very rare*
Anti-c (anti-hr')	80	20	16	Occasional
Anti-E (anti-rh'')	30	70	21	Occasional
Anti-e (anti-hr'')	97	3	3	Very rare

* Anti-C occurs more frequently along with anti-D, in which case it is produced by an Rh- individual.

TABLE II

	Anti-D	Anti-d	%	Incidence of Gene
DD (homozygous).....	+	o	37	$\sqrt{37} = 6.1$
Dd (heterozygous).....	+	+	48	
dd (homozygous).....	o	+	15	$\sqrt{15} = 3.9$

the two genes which in their several combinations form the three types, are given in Table III.

Given the frequency of a positive or negative reaction with, e.g., anti-D serum, the values of the corresponding Hr reactions can be derived from the following simple formulae:

1. $D + d = 10$
2. $D + 3.9 = 10$
3. $10 - 3.9 = 6.1$
4. $(D + d)^2 = (6.1 + 3.9)^2 = 37 + 48 + 15 = 100$

Similar calculations can be made for the C-c system in which the incidence of heterozygous types is 53 per cent and for E-e 27 per cent.

Of the six properties, the most important factor is D or Rh₀ and it is significant historically that this factor was described independently by Levine and Stetson in 1939 and Landsteiner and Wiener in 1940. The

former workers dealt with an agglutinin of human origin and the antigenic stimulus was believed to be derived from the transplacental transfer of fetal blood while the latter workers demonstrated the heterogenetic relationship of a factor common to human and rhesus blood, and first used the term "Rh."

A statistical study revealed that the blood cells of about 93 per cent of all mothers who deliver infants suffering from hemolytic disease of the newborn fail to react with anti-D or anti-Rh₀, and subsequent studies showed that their serum contains anti-D antibodies (agglutinins or blocking antibodies).^{2,5,6} Similarly, almost all patients suffering from intra-group transfusion reactions are Rh negative. It is for this reason that all screening tests are done with anti-D (anti-Rh₀) diagnostic sera. From the point of view of diagnosis of hemolytic disease of the newborn and prevention of isoimmuni-

TABLE III—THE CLINICALLY IMPORTANT EIGHT BLOOD TYPES

Serum A (anti-B).....	o		o		+		+	
Serum B (anti-A).....	o		+		o		+	
Group.....	O		A		B		AB	
Incidence in White Race.....	45		41		10		4	
	38	7	35	6	8.5	1.5	3.4	0.6
Reactions with anti-D: Rh	+	—	+	—	+	—	+	—

zation and intra-group transfusion accidents, it is important for the clinician to think in terms of eight instead of four blood groups. These relationships are shown in Table III.

Irrespective of the reactions with the five other Rh-Hr sera, the 85 per cent of individuals whose blood contains the Rh factor will be designated as Rh+ while the remaining 15 per cent will be referred to as Rh—. In contrast to the scheme of the four blood groups, the serum of the Rh— individual does not normally contain the corresponding antibody which must be produced in response to the antigenic stimulus of Rh+ blood.

The data in Table I indicate that the factor D is far more antigenic than the sum total of the five other antigens. Excluding the rare instance of isoimmunization by the A or B factors, one may state that the D factor is more antigenic by the value of $\frac{93}{7}$

or at least 13 times more so than all other Rh-Hr factors. This is all the more remarkable since four of the incompatible matings (d, E, C and c) occur more frequently than the mating incompatible for D.

The various types of Rh+ and Rh— individuals and their nomenclatures are given in order of their frequency in the white population.

Rh+	1. DCe	Rh ₁	54
	2. DcE	Rh ₁ Rh ₂	15
	3. DCE	Rh ₂	14
	4. Dce	Rh ₃	2
Rh—	5. dce	rh	13.0
	6. dCe	rh'	1.5
	7. dcE	rh''	0.5
	8. dCE	rh'rh''	Very rare

From the point of view of the clinician, the significance of these subtypes has been unnecessarily overemphasized because the only serum available for routine testing is anti-D, and the use of this one serum will detect at least 93 per cent of potential isoimmunization. For the protection of Rh— patients who may have produced anti-C as well as anti-D, suitable compatibility tests carried out with at least two random Rh— donors will be satisfactory. Should anti-C and anti-E sera also be available, it is necessary to test only the Rh— donors and to exclude types 6, 7 and 8 as donors for immunized Rh— patients. They may safely be used, at least once, for Rh— patients who have not yet been immunized.

The final analysis of Rh+ individuals may be confined to husbands of Rh— women in order to determine their genotype and to prevent transfusion reactions in those rare instances (about 7 per cent) in which Rh+ patients may have produced any one of the five other varieties of antibodies.

Unfortunately, the serum required for the direct determination of the genotype, anti-d (anti-Hr_o), occurs very rarely so that it is necessary to resort to indirect methods. In brief, these are based on the frequency of certain gene combinations in the general population. For example, an Rh+ individual of type Rh₁ is homozygous for the D factor if his blood fails to react with anti-c (anti-hr'). Thus, his genotype is represented as *DCE/DCe*. This method will fail if the rare combination *dCe* is contributed by one of his parents. Similarly, individuals of type Rh₁Rh₂ are most frequently formed from the common gene combination *DCE* (Rh₁) and *DcE* (Rh₂).

Since each contributes the gene *D*, he must be homozygous for factor *D* even though he is at the same time heterozygous for the clinically less important factor *C*.

If anti-d sera were generally available for the differentiation of genotypes *DD* and *Dd*, the role of the other two Rh-Hr systems (*C-c* and *E-e*) would become far less important, and their clinical application could then be limited to the analysis of the 7 per cent Rh+ mothers of affected infants or patients immunized by repeated transfusions.

Detection of Isoimmunization: Two main sorts of Rh-Hr antibodies are recognized; 1) those which directly agglutinate saline suspended cells, and 2) those which specifically unite with their corresponding antigen but fail to cause a visible reaction. As shown by Diamond and Wiener, the latter type of antibody will give direct agglutination if the test cells are suspended in serum or 20-30 per cent bovine albumin. Coombs' has shown that the specific union of antigen and antibody can be detected if the thoroughly washed cells are tested with an absorbed anti-human precipitin prepared in rabbits or other suitable animals. Clumping results from the specific reaction of the globulin-containing antibody on the surface of the red cells, which serves as antigen and the anti-human globulin present in the precipitin serum.

Great confusion has resulted from the arbitrary use of a variety of terms for the two sorts of antibodies. These are listed below:

Agglutinins	Agglutinoids (glutinins)
Saline agglutinins	Albumin agglutinins
Heat-labile antibodies	Heat-stable antibodies
Complete antibodies	Incomplete antibodies
Bivalent antibodies	Univalent antibodies
Early antibodies	Late antibodies
	Cryptagglutinoids
	Conglutinins
	Blocking antibodies
	Coating antibodies

Tests for the detection of isoimmunization should be carried out in all prenatal cases and for all candidates for transfusion, Rh+ as well as Rh-. The test blood should be so selected that all six Rh-Hr antigens are present, such as in a mixture of two group O bloods, types Rh₁ and Rh₂.

From a practical standpoint, two methods may be employed in routine tests—the slide test or the test tube. The former is suitable for small scale work or in urgent cases while the test tube method is preferable for simultaneous tests of numerous sera.

For the slide test, about 40-50 per cent suspension of the test blood such as is present in (dry) oxalated blood should be employed. One drop of the patient's serum is mixed with one or two small drops of the test blood on a slide which is placed on a warm illuminated glass surface and rocked slowly from side to side.

For the tube method, it is desirable to test all sera with both saline and albumin suspended test cells. A more dilute suspension may be used (2-5 per cent). Readings may be made at the end of 1 to 2 hours' incubation. The presence of agglutinins is indicated by reactions in both tubes while the so-called blocking antibody will react only with the albumin suspended cells.

After the readings with the saline suspended cells are completed, the Coombs test should be carried out to detect specific coating. Each of the tubes is filled with saline and the cells are then washed at least three times, after which two drops of a processed and standardized anti-human precipitin is added.

The results with the Coombs test will serve to confirm the findings with the direct reaction with albumin suspended cells. At the same time, it will aid in the detection of so-called prozones due to the presence of both agglutinins and blocking antibodies in the same serum or due to the presence of several varieties of blocking or incomplete antibodies.⁵

No suitable substitutes for bovine albumin have been found. The several hydrophilic colloids (pectin, acacia, gelatin, polyvinyl alcohol) have the unfavorable property of inducing very strong pseudo-agglutination.⁹ In titration of blocking antibodies, it

is preferable to use pooled normal male serum as a diluent and albumin suspended cells. A combination of serum and albumin in these tests gives stronger reactions and higher titers than serum-serum mixtures or albumin-albumin mixtures.¹⁰

In the tests for detection of isoimmunization, 30 per cent albumin as the suspended medium for the test cells gives stronger reactions than 20 per cent albumin.¹⁰ Furthermore, prozone-containing sera will give at least weak reactions in the qualitative test with the greater concentration of bovine albumin. The writer, however, prefers to use 20 per cent bovine albumin which is less viscous, provided that the Coombs reaction is carried out on the saline suspended cells in order to detect prozones.

Once an antibody is detected, additional tests are required to determine its potency (by titration), its specificity in tests with cells of known antigenic structure and its avidity. All attempts should be made to collect large quantities of sera containing potent antibodies of the several varieties which will be useful for routine Rh-Hr testing and for determination of genotypes. More recently, attempts have been made to immunize donors on a voluntary basis and to stimulate the formation of potent antibodies in already immunized mothers who may have been sterilized or do not plan further pregnancies.

The normal iso-antibodies, anti-A and anti-B in all anti-Rh or anti-Hr sera, must be removed either by absorption with suitable cells or preferably by the addition of soluble A and B substances.

The Coombs reaction is of greatest value in testing the cord or capillary blood in order to determine if the infant's red blood cells are specifically "coated" with maternal antibodies. Curiously enough, only blocking antibodies but not agglutinins can be demonstrated on the surface of the infant's red blood cells. Strongly coated red blood cells, as indicated by a powerful reaction with the Coombs reagent, will fail to react with anti-D agglutinins and have been erroneously diagnosed as Rh—. Actually, such blood is Rh+ and fails to react because all Rh receptors have been saturated for long periods in vivo with maternal

antibodies.

No attempt will be made here to correlate the serological findings with the prognosis in the infant, except to state that the presence of a positive Coombs reaction on the cord cells of an immunized Rh—mother does not by itself constitute an indication for a replacement transfusion. In general, the severity of the condition of the infant depends upon the length of the period of intrauterine passage of antibodies into the fetal circulation. Unfortunately, little is known of the factors which influence the transfer of the several varieties of antibodies across the placental barrier.

Mechanism of Transplacental Transfer: Isoimmunization by the Rh factor in fetal blood assumes an importance altogether out of its proportion to the low incidence of hemolytic disease because it is the first example in any species of a new cause of fetal and neonatal morbidity attributable to a genetic difference involving a particular blood factor which has a normal incidence in any racial group. In this connection, it is of interest that the incidence of hemolytic disease is lower in negroes (about 5-8 per cent Rh—, instead of 15 per cent and almost never observed in Chinese, Japanese or American Indians (less than 1 per cent Rh—).⁹

It is assumed that in every normal pregnancy a few fetal red blood cells find their way into the maternal circulation, at least in sufficient quantity to induce isoimmunization. This passage probably begins in the latter half of the pregnancy when the fetal blood vessels gradually become larger and, over an ever-expanding surface area, gradually approach the maternal sinuses from which they are then separated by a single layer of syncytial cells, aside from the endothelium. Other favorable circumstances are the sluggish circulation in the maternal sinuses and the greater pressure in the fetal circulation due to heart action and further increased by active fetal movement in the latter half of the pregnancy.

It is significant that the Rh factor does not occur in a water-soluble form and it is probably limited to the red blood cells, only small quantities of which suffice for

antibody production. The important role of transplacental transfer of fetal red blood cells is illustrated in those instances in which the firstborn infant is affected. In the vast majority of these cases, the Rh—mother had previously been transfused and the appearance of antibodies in the latter third of the pregnancy can be interpreted only as the response to antigenic material received in the course of the pregnancy. These cases serve as examples of the specific anamnestic reaction since antibodies resulting from the transfusion of perhaps 10-15 years previously have since disappeared, but they reappear more rapidly in response to the same antigenic stimulus many years later.

Additional evidence to indicate that there is no need to assume gross pathologic lesions in the placenta will be found in the recent papers of Naeslund and Aren, Kline and Everett and Henderson.* It would indeed be remarkable if nature provided an absolutely perfect organ which, like a malignant cell, is endowed with such invasive properties and rapid proliferation that in the short space of 40 weeks it attains a surface area of 70-120 square feet essential for the nourishment of the fetus.

Undoubtedly, further studies will reveal many examples of isoimmunization by fetal blood in other species of animals, especially those characterized by a type of placenta which does not differ much from that in man. Curiously enough, the first successful demonstration was in horses in which there

are four layers of tissue cells separating the two circulations. Because maternal antibodies of the mare do not pass into the fetus, the disease does not occur in utero but only after ingestion of colostrum which is so rich in antibodies.^{12, 13}

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Recent Views on the Genetics of the Rh-Hr Blood Factors

HERLUF H. STRANDSKOV

At least 6 Rh-Hr antigens are known to exist. Credit for their discovery must be given to Landsteiner and Wiener, Levine, Race, Mourant, and Diamond. Originally the 6 antigens were called Rh', Hr', Rh₀, Hr₀, Rh" and Hr". In 1944 the British investigators, Fisher and Race, introduced

another set of names known as the CDE system. Because of its simplicity and descriptiveness this system is gaining favor with many investigators, not only in Europe but in the Americas as well. It is the system which I personally prefer, primarily because I teach large classes in human

genetics and find that it is much more readily accepted by students. I should, however, like to see the symbol Rh shown before the CDE letters whenever it might not otherwise be clear that reference is being made to an Rh antigen. The two sets of symbols which have been proposed are shown in Table I.

TABLE I—NAMES OF RH-HR ANTIGENS

<i>Original names</i>	<i>Fisher-Race symbols</i>
Rh' and Hr'	Rh C and Rh c
Rh ₀ and Hr ₀	Rh D and Rh d
Rh'' and Hr''	Rh E and Rh e

As is indicated in Table I the 6 antigens exist in pairs. A member of a given pair may occur without the other member in the blood of a given individual, or in combination with the other one. Hence with respect to each pair, 3 blood types are possible. Each of the 3 possible blood types relative to a given pair may exist in combination with each of the 3 possible types of each of the 2 other pairs. Accordingly 27 Rh-Hr blood types are possible. These 27 types may be designated by the original names, by the letters of Fisher and Race or by a set of abbreviated symbols advocated by Wiener. As I have already indicated, I personally prefer the CDE system but with the symbol Rh appearing before the blood type if it is not immediately clear that reference is being made to an Rh type. The original names are cumbersome and the abbreviated names of Wiener are not descriptive. The latter may be perfectly acceptable as abbreviations in a particular laboratory but in my opinion they are not the most acceptable for general use. The CDE system corresponds closely to the A-B or M-N terminology in indicating exactly the antigen present in the blood.

Landsteiner and Wiener were the first to report on the inheritance of the Rh blood factor. This was in 1941 when only 1 antigen was known, namely the one now called Rh₀ or D. These two investigators

TABLE II—THE 27 RH-HR BLOOD TYPES

<i>Blood type using the original names of the antigens</i>	<i>Recommended names</i>
1. Rh' Rh ₀ Rh''	Rh CDE
2. Rh' Rh ₀ Rh''Hr''	Rh CDEe
3. Rh' Rh ₀ Hr''	Rh CDe
4. Rh' Rh ₀ Hr ₀ Rh''	Rh CDdE
5. Rh' Rh ₀ Hr ₀ Rh'' Hr''	Rh CDdEe
6. Rh' Rh ₀ Hr ₀ Hr''	Rh CDde
7. Rh' Hr ₀ Rh''	Rh CdE
8. Rh' Hr ₀ Rh'' Hr''	Rh CdEe
9. Rh' Hr ₀ Hr''	Rh Cde
10. Rh' Hr' Rh ₀ Rh''	Rh CcDE
11. Rh' Hr' Rh ₀ Rh'' Hr''	Rh CcDEe
12. Rh' Hr' Rh ₀ Hr''	Rh CcDe
13. Rh' Hr' Rh ₀ Hr ₀ Rh''	Rh CcDdE
14. Rh' Hr' Rh ₀ Hr ₀ Rh'' Hr''	Rh CcDdEe
15. Rh' Hr' Rh ₀ Hr ₀ Hr''	Rh CcDde
16. Rh' Hr' Hr ₀ Rh''	Rh CcdE
17. Rh' Hr' Hr ₀ Rh'' Hr''	Rh CcdEe
18. Rh' Hr' Hr ₀ Hr''	Rh Ccde
19. Hr' Rh ₀ Rh''	Rh cDE
20. Hr' Rh ₀ Rh'' Hr''	Rh cDEe
21. Hr' Rh ₀ Hr''	Rh cDe
22. Hr' Rh ₀ Hr ₀ Rh''	Rh cDdE
23. Hr' Rh ₀ Hr ₀ Rh'' Hr''	Rh cDdEe
24. Hr' Rh ₀ Hr ₀ Hr''	Rh cDde
25. Hr' Hr ₀ Rh''	Rh cdE
26. Hr' Hr ₀ Rh'' Hr''	Rh cdEe
27. Hr' Hr ₀ Hr''	Rh cde

postulated that a dominant autosomal gene existed which was responsible for the then known antigen. As this hypothesis was originally presented an individual who was Rh positive (Rh+) was either homozygous dominant, Rh Rh, or heterozygous, Rh rh; whereas an individual who was Rh negative (Rh-) was homozygous recessive, rh rh. The genetic results expected according to this original hypothesis are shown in Table III.

When Levine discovered the first Hr antigen, now called Hr' or c, it became apparent that the original hypothesis of a dominant and a recessive allele could no longer be defended, at least, not in its entirety, because the so-called recessive gene

TABLE III—LANDSTEINER-WIENER
GENETIC HYPOTHESIS (1941)

<i>Genes</i>	<i>Genotypes</i>	<i>Phenotypes</i>
Rh	Rh Rh	Rh positive (Rh+)
rh	Rh rh	
	rh rh	
		Rh negative (Rh—)
<i>Possible matings</i>	<i>Phenotypic ratio expected</i>	
1. Rh Rh x Rh Rh	1 Rh+	
2. Rh Rh x Rh rh	1 Rh+	
3. Rh Rh x rh rh	1 Rh+	
4. Rh rh x Rh rh	$\frac{3}{4}$ Rh+ : $\frac{1}{4}$ Rh—	
5. Rh rh x rh rh	$\frac{1}{2}$ Rh+ : $\frac{1}{2}$ Rh—	
6. rh rh x rh rh	1 Rh—	

was found to produce an antigen and found to be as dominant as its allele. In other words, no dominance or equal dominance was found to exist. The results relative to the inheritance of Rh' and Hr' might then have been presented as shown in Table IV.

TABLE IV—GENETIC HYPOTHESIS
FOLLOWING DISCOVERY OF Hr'
(Rh c) BY LEVINE

<i>Genes</i>	<i>Genotypes</i>	<i>Phenotypes</i>
Rh ^c	Rh ^c Rh ^c	Rh C
Rh ^c	Rh ^c Rh ^c	Rh Cc
	Rh ^c Rh ^c	Rh c
<i>Possible matings</i>	<i>Phenotypic ratio expected</i>	
1. Rh ^c Rh ^c x Rh ^c Rh ^c	1 Rh C	
2. Rh ^c Rh ^c x Rh ^c Rh ^c	$\frac{1}{2}$ Rh C : $\frac{1}{2}$ Rh Cc	
3. Rh ^c Rh ^c x Rh ^c Rh ^c	1 Rh Cc	
4. Rh ^c Rh ^c x Rh ^c Rh ^c	$\frac{1}{4}$ Rh C : $\frac{2}{4}$ Rh Cc : $\frac{1}{4}$ Rh c	
5. Rh ^c Rh ^c x Rh ^c Rh ^c	$\frac{1}{2}$ Rh Cc : $\frac{1}{2}$ Rh c	
6. Rh ^c Rh ^c x Rh ^c Rh ^c	1 Rh c	

In Table IV the two alleles are designated by the basic locus symbol Rh and distinguished by the superscripts C and c. This is in accordance with a proposal which will be presented later for the symbols of all Rh genes. It should be noted especially that the phenotypic ratios shown in Table IV differ in certain instances from those shown in Table III.

As the second, third and fourth antigens were reported by various investigators and shown to have a hereditary basis, Wiener postulated that the genes responsible for all of these variations occupied a single locus, in other words, that a series of multiple alleles existed. He now assumes at least 8 alleles.

In 1941 Fisher and Race proposed a 3 linked-loci hypothesis with crossing over occurring or having occurred between the 3 loci. According to this hypothesis 8 homologous chromosomes, each with a different gene combination, may exist in a population. Fisher and Race have given the 3 pairs of genes the same names as the corresponding antigens, namely, C and c, D and d, and E and e. In my opinion this usage is an unfortunate one. If the 3 locus hypothesis should prove to be the correct one it would be preferable to use Rh as the basic locus symbol for all three loci and the letters CDE as superscripts. One specific objection to the use of C as a locus symbol is that it has previously been used in mammalian genetics, including human, for a locus affecting skin pigmentation or skin color. The 8 possible gene combinations on chromosomes, which are postulated by the 3 locus hypothesis, are shown in Table V.

As additional antigens were discovered and shown to be inherited, Wiener proposed symbols for the additional alleles which he assumed to exist. These symbols he has changed from time to time but his most recent set is probably that shown in Table V. In the opinion of many investigators, even those who favor the 8 allele hypothesis, these gene symbols proposed and strongly defended by Wiener are not fortunate choices. Among the arguments advanced against them is that they are not descriptive or suggestive of the actions which the alleles produce. Furthermore, they are not

TABLE V—GENE SYMBOLS

8 allele hypothesis		3 locus hypothesis		
<i>Gene symbols of 8 alleles</i>		<i>8 Gene combinations on chromosomes</i>		
<i>Wiener</i>	<i>Strandkov</i>			
Rz	Rh ^{CDE}	Rh ^C	Rh ^D	Rh ^E
R ¹	Rh ^{CDe}	Rh ^C	Rh ^D	Rh ^e
r ^y	Rh ^{CdE}	Rh ^C	Rh ^d	Rh ^E
r'	Rh ^{Cde}	Rh ^C	Rh ^d	Rh ^e
R ²	Rh ^{cDE}	Rh ^c	Rh ^D	Rh ^E
R ^o	Rh ^{cDe}	Rh ^c	Rh ^D	Rh ^e
r''	Rh ^{cdE}	Rh ^c	Rh ^d	Rh ^E
r	Rh ^{cde}	Rh ^c	Rh ^d	Rh ^e

easily presented in long hand or in print without error. For example, the prime superscript and number 1 superscript are easily mistaken. Finally the use of some capital letters and some lower case letters is not in accordance with accepted genetic rules when no dominance or equal dominance of the alleles exists. Because of the numerous objections to Wiener's symbols which have been advanced I have proposed the use of Rh as the basic locus symbol and C D E letters as superscripts. In the proposed system the superscripts indicate specifically the antigens produced by each gene, if the 8 allele hypothesis is the correct one. Nearly the only valid argument in favor of Wiener's symbols is that they have priority. This argument deserves considerable consideration but we must also remember that whatever system is adopted now will be used for all time to come. Hence any one system should not be adopted lightly.

According to the 8 allele hypothesis 36 genotypes are possible. However, only 27 phenotypes or blood types should be produced, because some of the genotypes give duplicate phenotypes. The 36 genotypes and 27 phenotypes using both Wiener's symbols and those proposed by me are presented in Table VI. Only 27 genotypes are possible according to the 3 locus hypothesis. These are not shown in Table VI because they may be read directly from the 27 pheno-

types which are indicated by the use of the CDE system of letters.

Since two hypotheses have been proposed to account for the inheritance of Rh-Hr blood types, and neither one is universally accepted, attempts have been made to determine which one is the correct one. To do so is not easy, but several types of discriminating evidence are possible. I shall mention and discuss briefly three of these possible lines, namely: 1) serological evidence, 2) cross-over results, and 3) gene, genotypic and phenotypic frequency analyses.

The possibly discriminating serological evidence is of the following type. According to the 8 allele hypothesis each gene is capable of producing 3 different antigens, whereas according to the 3 locus hypothesis each gene is responsible only for a single antigen. If we examine the action of other human genes which are known to be responsible for the production of antigens we find that each gene is responsible for the production of only 1 antigen. This at least is true of the genes responsible for A-B and M-N antigens. This is the simplest relationship imaginable and, therefore, seemingly the most probable. It does not follow, however, that the other relationship is impossible, namely, that a single gene can effect the production of 3 separate antigens as the 8 allele hypothesis assumes. Thus it will be apparent that it is my opinion that the serological evidence favors the 3 locus hypothesis but not to the extent of ruling out the 8 locus hypothesis.

The possible genetic evidence which may discriminate between the two proposed hypotheses is, as I have already stated, of two major types, namely 1) cross-over evidence, and 2) evidence obtained from an analysis of gene, genotypic and phenotypic frequencies in populations.

Cross-over evidence should be obtainable from a study of mating results if the 3 locus hypothesis is the correct one. By cross-over results is meant evidence that genes have been exchanged between homologous chromosomes in meiosis. To illustrate the results expected if crossing over occurs, let us assume a female of blood type Rh CcDdEe and who received the gene or genes responsible for the antigens C, D and

TABLE VI—GENOTYPES AND PHENOTYPES EXPECTED ACCORDING TO 8 ALLELE HYPOTHESIS

<i>Proposed symbols (Strandskov)</i>		<i>Wiener symbols</i>	
<i>Genotypes</i>	<i>Phenotypes</i>	<i>Genotypes</i>	<i>Phenotypes</i>
1. Rh ^{CDE} Rh ^{CDE}	1. Rh CDE	1. R ^z R ^z	1. R _z R _z
2. Rh ^{CDE} Rh ^{CDe}	2. Rh CDEe	2. R ^z R ¹	2. R _z R ₁
3. Rh ^{CDe} Rh ^{CDE}	3. Rh CDe	3. R ¹ R ¹	3. R ₁ R ₁
4. Rh ^{CDE} Rh ^{CdE}	4. Rh CDdE	4. R ^z r ^y	4. R _z r _y
5. Rh ^{CDE} Rh ^{Cde} or Rh ^{CdE} Rh ^{CDE}	5. Rh CDdEe	5. R ^z r ['] or r ^y R ¹	5. R _z r [']
6. Rh ^{CDe} Rh ^{Cde}	6. Rh CDde	6. R ¹ r [']	6. R ₁ r [']
7. Rh ^{CdE} Rh ^{CdE}	7. Rh CdE	7. r ^y r ^y	7. r _y r _y
8. Rh ^{CdE} Rh ^{Cde}	8. Rh CdEe	8. r ^y r [']	8. r _y r [']
9. Rh ^{Cde} Rh ^{Cde}	9. Rh Cde	9. r ['] r [']	9. r ['] r [']
10. Rh ^{CDE} Rh ^{CDE}	10. Rh CcDE	10. R ^z R ²	10. R _z R ₂
11. Rh ^{CDE} Rh ^{Cde} or Rh ^{CdE} Rh ^{CDE}	11. Rh CcDEe	11. R ^z R ⁰ or R ¹ R ²	11. R _z R ₀
12. Rh ^{CDe} Rh ^{CDE}	12. Rh CcDe	12. R ¹ R ⁰	12. R ₁ R ₀
13. Rh ^{CDE} Rh ^{CdE} or Rh ^{CdE} Rh ^{CDE}	13. Rh CcDdE	13. R ^z r ["] or r ^y R ²	13. R _z r ["]
14. Rh ^{CDE} Rh ^{cde} or Rh ^{CDE} Rh ^{cDE} or Rh ^{CdE} Rh ^{Cde} or Rh ^{CDE} Rh ^{Cde}	14. Rh CcDdEe	14. R ^z r or R ¹ r ["] or r ^y R ⁰ or R ² r [']	14. R _z r
15. Rh ^{Cde} Rh ^{cde} or Rh ^{Cde} Rh ^{Cde}	15. Rh CcDde	15. R ¹ r or R ⁰ r [']	15. R ₁ r
16. Rh ^{CdE} Rh ^{cDE}	16. Rh CcdE	16. r ^y r ["]	16. r _y r ["]
17. Rh ^{CdE} Rh ^{cde} or Rh ^{Cde} Rh ^{cDE}	17. Rh CcdEe	17. r ^y r or r ['] r ["]	17. r _y r
18. Rh ^{Cde} Rh ^{cde}	18. Rh Ccde	18. r ['] r	18. r ['] r
19. Rh ^{CDE} Rh ^{cDE}	19. Rh cDE	19. R ² R ²	19. R ₂ R ₂
20. Rh ^{CDE} Rh ^{cDe}	20. Rh cDEe	20. R ² R ⁰	20. R ₂ R ₀
21. Rh ^{Cde} Rh ^{cDe}	21. Rh cDe	21. R ⁰ R ⁰	21. R ₀ R ₀
22. Rh ^{CDE} Rh ^{cDE}	22. Rh cDdE	22. R ² r ["]	22. R ₂ r ["]
23. Rh ^{CDE} Rh ^{cde} or Rh ^{cDE} Rh ^{CDE}	23. Rh cDdEe	23. R ² r or r ["] R ⁰	23. R ₂ r
24. Rh ^{Cde} Rh ^{cde}	24. Rh cDde	24. R ⁰ r	24. R ₀ r
25. Rh ^{cDE} Rh ^{cDE}	25. Rh cdE	25. r ["] r ["]	25. r ["] r ["]
26. Rh ^{cDE} Rh ^{cde}	26. Rh cdEe	26. r ["] r	26. r ["] r
27. Rh ^{cde} Rh ^{cde}	27. Rh cde	27. rr	27. rr

E from one of her parents, and the gene or genes responsible for the antigens, c, d, and e from her other parent. Her genetic composition might then be represented as CDE/cde, without implying that either hypothesis is the correct one. Now if she should marry a man Rh cde who may be represented as cde/cde, and they should have children, then evidence of crossing over would exist if children were born

with blood types Rh Ccde, Rh cDde, Rh cdEe as well as children of blood types Rh CcDdEe and Rh cde. If no crossing over occurred then only children of the two latter blood types should be born to such a set of parents.

A large number of parents and their children have been studied for evidence of crossing over but none has been found so far. Race (1948) states that he has tested

over 150 families without detecting crossing over. Wiener and others likewise have studied many families and have found no evidence of crossing over. Hence if crossing over does occur it must be relatively rare. Thus it is apparent that the family studies presented so far give negative evidence in favor of the 3 locus hypothesis and are in agreement with the 8 allele hypothesis. They, therefore, may be said to favor the latter hypothesis. Perhaps we should mention that a single child suggesting crossing-over would not be sufficient evidence for the 3 locus hypothesis. The single observed result might represent a mutation rather than a cross-over. Only if cross-overs on a fairly large scale are observed can the evidence be said to rule out the 8 allele hypothesis and establish the 3 locus hypothesis. Fisher has suggested that indirect evidence of crossing over exists from an analysis of combinations of antigens in populations but this line of evidence, at least as advanced so far, is not very convincing.

The evidence in favor of either of the two proposed hypotheses based on observed gene, genotypic and phenotypic frequencies in populations is somewhat complex and cannot be dealt with in detail here but perhaps we may outline a few of the more direct lines of reasoning. By examining fairly large numbers of individuals in several different populations Wiener has obtained evidence that observed phenotypic frequencies agree fairly closely with frequencies expected on the basis of the 8 allele hypothesis. The British workers have been interested in comparing observed gene combinations on chromosomes with expected frequencies. They do not, however, assume that crossing has occurred to the extent that the genes at the different loci have reached combination frequencies comparable to random assortment. This is usually what would be expected if crossing over had occurred at all between the 3 loci. Rife has recently tested the 3 locus hypothesis by examining phenotypic frequencies on the assumption that equilibrium gene combinations have been reached. He finds that the observed phenotypic frequencies do not agree with those expected when this assumption is made. In other words he con-

cludes that observed phenotypic frequencies do not agree closely with those expected on the basis of a 3 locus hypothesis. It must be admitted, however, that the test as applied may not be completely valid without a consideration of the role of selection or the make up of the sample population which was tested. Nevertheless, it seems that the gene, genotypic and phenotypic frequency analyses made so far favor on the whole the 8 allele hypothesis of Wiener rather than the 3 locus hypothesis of Fisher and Race.

SUMMARY

The following statements appear permissible relative to the genetics of the Rh-Hr Blood Factors.

1. The Rh-Hr blood types are completely genetically determined, that is, there is always a complete correspondence between phenotype and genotype.

2. An individual does not have an Rh-Hr antigen in his blood which is not present in at least one of his parents.

3. Neither of the two genetic hypotheses proposed to account for the inheritance of the Rh-Hr blood types has been completely established at the present time. The majority of the evidence, however, appears to favor the 8 allele hypothesis of Wiener rather than the 3 locus hypothesis of Fisher and Race.

4. Despite the fact that neither genetic hypothesis has been established, Rh-Hr blood tests may be used as evidence in legal cases of disputed paternity or baby mix up. However, evidence based on mode of inheritance must not be used.

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Medicolegal Aspects of the Rh-Hr Blood Types

ALEXANDER S. WIENER

It was originally intended to confine this paper to the medicolegal applications of the Rh-Hr types, but I find that in order to make the subject intelligible it is necessary first to review the serology and genetics of the A-B-O blood groups and the M-N types. While it is true that the Rh-Hr types are more complicated than the A-B-O groups or the M-N types, the principles involved are the same, and knowledge of the facts and of the problems relating to the A-B-O and M-N types facilitates mastering the Rh-Hr blood types. Also the supposed simplicity of the A-B-O groups and the M-N types has been overemphasized, because when all the facts known concerning these two systems are taken into account the situation is no longer simple. In view of the clinical importance of the Rh-Hr types, the physician is constantly confronted with all the intricacies of this system while he is not compelled to learn the more refined facts concerning the other systems. The serologist and the medicolegal expert, however, must know the facts in their entirety.

TABLE I—THE FOUR LANDSTEINER BLOOD GROUPS

<i>Blood groups (Phenotypes)</i>	<i>Reactions of blood cells with serums</i>	
	<i>Anti-A</i>	<i>Anti-B</i>
O.....	—	—
A.....	+	—
B.....	—	+
AB.....	+	+

In Table I we have summarized the reactions given by human red blood cells when tested with anti-A serum and anti-B serum, determining the four Landsteiner blood groups. This represents about all that the average physician is required to know concerning this subject, which accounts for its apparent simplicity. As will be pointed out shortly, however, the situation is actually far more complicated. At this point, it should be emphasized that for medicolegal

work all blood tests should be carried out at least in duplicate and preferably in quadruplicate, using as controls blood specimens of known groups and types. In the case of the blood groups, the reciprocal relationship between the iso-agglutinins in the serum and the agglutinogens in the red cells (Landsteiner's rule), except during the neonatal period, supplies an additional method of checking the worker's results, and tests for the agglutinin content of the serum are an essential part of the examination in order to further guarantee the accuracy of the results.

To account for the heredity of the blood groups, a number of theories were proposed, namely, inheritance by two independent pairs of allelic genes A-a and B-b (von Dungern and Hirsfeld); inheritance by two pairs of genes either completely or partly linked (Furuhata, Bauer); or inheritance by a series of multiple allelic genes (Bernstein). The existence of separate pairs of genes for A and B, A-a and B-b, was readily disproved by Bernstein because this would imply that the distribution of the four blood groups would satisfy the following relation: $O \times AB = A \times B$. Since in New York City, for example, the approximate frequencies of the four groups are group O, 40 per cent; group A, 40 per cent; group B, 15 per cent; and group AB, 5 per cent, it is obvious that the equation does not hold. On the other hand, the theory of multiple alleles was proved to be correct by studies on families as well as by statistical analysis of the distribution in the general population.

As suggested by Strandkov, the three allelic genes postulated by Bernstein may be designated as I^A , I^B , and I^O , respectively, and this conforms with the practice of geneticists to use a common base symbol for all genes of the same allelic series. The symbol " I " was selected as a base symbol to represent "isoagglutinin." These designations also have the advantage that the symbols for the genes, which incidentally are printed in italics, are quite distinct from the symbols for the corresponding agglutinogens, so that there is no ambiguity between the designations of phenotypes and genotypes. It is clear that according to

TABLE II—THE A-B-O PHENOTYPES AND GENOTYPES

<i>Phenotypes</i>	<i>Genotypes</i>
O.....	$I^O I^O$
A.....	$I^A I^A$ and $I^A I^O$
B.....	$I^B I^B$ and $I^B I^O$
AB.....	$I^A I^B$

Bernstein's theory, corresponding to the four phenotypes there are six genotypes possible, as shown in Table II. Since here we are interested only in the medicolegal applications, the results of Bernstein's theory are summarized in the following two laws:

1. The agglutinogens A and B cannot appear in the blood of a child unless present in the blood of one or both parents.

2. Group AB parents cannot have group O children, and group O parents cannot have group AB children.

As has been indicated above, however, the situation is actually far more complicated. Firstly, there exist variants of the agglutinin A, the most important of which are designated as A_1 and A_2 , respectively. Rarely, additional variants designated as A_3 and A_4 have been encountered, as well as variants which give reactions intermediate between A_1 and A_2 . Similar variants of agglutinin B probably exist also, but these are less sharply defined so that a satisfactory technique for demonstrating them has not yet been devised. Moreover, the blood group O is not merely characterized by the absence of agglutinogens A and B, but also by the presence in the red cells of a special agglutinin O which is shared also by all bloods of subgroup A_2 . Finally, there is also evidence for a property C shared by agglutinin A_1 and B. Omitting the rare variants A_3 , A_4 , etc., these facts have been summarized in Table III. Because of limitations of space, it is not possible here to go into further details concerning the concepts presented in this table. It may be of interest, however, to summarize the medicolegal implications of the subgroups of A, according to the following two laws:

TABLE III—THE A-B-O SERIES OF GENES AND THE REACTIONS THEY DETERMINE

Genes	Corresponding agglutino-gen	Reactions with serums				
		Anti-A ₁	Anti-A	Anti-B	Anti-C	Anti-O
I ^A	A ₁	+	+	—	+	—
I ^B	B	—	—	+	+	—
i ^A	A ₂	—	+	—	—	+
i ^o	O	—	—	—	—	+

1. No child can belong to subgroup A₁ or subgroup A₁B unless one or both parents belong to one of these subgroups. For example, two parents both of subgroup A₂ cannot have a child of subgroup A₁.

2. Parents of subgroups A₁B cannot have children of subgroup A₂, and parents of subgroup A₂ cannot have children of subgroup A₁B.

In the ordinary medicolegal cases where the blood group tests are applied a man is accused by a woman of the paternity of her child born out of wedlock, and he denies the charge. If the man has been falsely accused, by blood tests it may be possible to demonstrate his innocence, namely, if the groups of the man, the mother and her child do not satisfy the laws enunciated above. Obviously, the mere fact that the blood groups correspond is no proof that the accused man is the father, so that the tests can only be used to exclude paternity or maternity. The chances of exclusion will vary with the distribution of the blood groups in the population, and, among Caucasians, a falsely accused man has about one chance in six of establishing his innocence. The A₁-A₂ subgroups add only 1 to 2 per cent of the chances of exclusion, and for this reason as well as certain technical serological difficulties are but rarely applied to the court room.

A substantial step forward resulted from the discovery of the M-N blood types by Landsteiner and Levine in 1927. The fundamental facts concerning these blood types are even simpler than those of the blood groups, as can be seen from Table IV. Ex-

cept for certain rare exceptions, however, isoagglutinins for M and N do not exist in normal human serum, so that the antisera are usually prepared by immunizing rabbits. As Landsteiner and Levine pointed out, the existence of only three M-N types is readily explained by postulating their hereditary transmission by a simple pair of allelic genes, L^M and L^N, the base symbol L being selected in honor of Landsteiner, the father of blood grouping. The genetic implications of the theory are readily worked out since there is a one-to-one correspondence between genotypes and phenotypes (cf Table V), and there is ample statistical evidence from the study of families to confirm the accuracy of the theory. For the purpose of this paper, however, it is sufficient to summarize the results of the theory in the following two laws:

1. The agglutinogens M and N cannot appear in the blood of a child unless present in the blood of one or both parents.

2. Type M parents cannot have type N children, and type N parents cannot have type M children.

TABLE IV—THE THREE M-N TYPES

Blood types (Phenotypes)	Reactions of blood cells with serums	
	Anti-M	Anti-N
M	+	—
N	—	+
MN	+	+

TABLE V—THE M-N PHENOTYPES AND GENOTYPES

<i>Phenotypes</i>	<i>Genotypes</i>
M.....	<i>LMLM</i>
N.....	<i>LNLN</i>
MN.....	<i>LMLN</i>

With the combined use of the M-N types and the A-B-O groups, the chances of excluding paternity where a false accusation has been made are raised from 16 per cent to approximately 30 per cent. It might be pointed out that the chances are not simply additive because of the existence of cases with a double exclusion by both tests simultaneously. Therefore, no matter how many new tests are added it is impossible ever to attain the ideal of 100 per cent exclusion.

Also, in the cases of the M-N types, the true situation is actually not as simple as implied in Tables IV and V. Variants of the agglutinogens M and N have been found, but these are rare and of little practical importance. Recently, however, an important step forward was made when Race and Sanger discovered in the serum of the mother of an erythroblastotic baby, an irregular isoagglutinin for a new blood property designated by them as agglutinin S. Statistical and family studies proved this agglutinin to be related to the properties M and N. The existence of two variants in the agglutinin M was therefore demonstrated, one with and one without the property S, and similarly two variants of the agglutinin N were demonstrated to exist. Accordingly, instead of a pair of allelic genes, it is now necessary to postu-

late a series of a minimum of four allelic genes as shown in Table VI. The existence of a separate gene for the agglutinin S, linked to or independent of the genes for the agglutinogens M and N, was readily disproved by the use of the product serum referred to in connection with the A-B-O blood groups. For the present, however, the agglutinin S is not available for medicolegal use because of the scarcity of the required antiserum; besides, more family studies will have to be done before the medicolegal application becomes justifiable.

The reader who has absorbed the facts concerning the A-B-O groups and the M-N types will have no difficulty in understanding and learning the scheme of the 8 Rh types shown in Table VII. It will be noticed that the symbol for agglutinin Rh₀ is written with a large "R," while the symbols for agglutinogens rh' and rh" are written with a small "r." This is done in order to emphasize the special serological and genetic position of the agglutinin Rh₀. Agglutinin Rh₀ corresponds to the original rhesus factor discovered by Landsteiner and Wiener in 1937, with the aid of immune animal serums prepared by immunizing rabbits and guinea-pigs with the blood of rhesus monkeys. Nowadays the antisera are usually produced by immunizing volunteer male type rh donors, or obtained from patients who have had hemolytic transfusion reactions or erythroblastotic babies. With the aid of the human antisera it was demonstrated that three Rh factors exist instead of only one, designated as Rh₀, rh', and rh", respectively. The symbol Rh₀ is written with a capital "R" because Rh₀ is by far the most anti-

TABLE VI—THE M-N SERIES OF ALLELIC GENES

<i>Genes</i>	<i>Corresponding agglutinogens</i>	<i>Reactions with serums</i>		
		<i>Anti-M</i>	<i>Anti-N</i>	<i>Anti-S</i>
<i>LM</i>	M	+	—	—
<i>LM_s</i>	Ms	+	—	+
<i>LN</i>	N	—	+	—
<i>LN_s</i>	Ns	—	+	+

TABLE VII—THE EIGHT Rh BLOOD TYPES

Rh types (Phenotypes)	Reactions with serums		
	Anti-rh'	Anti-rh''	Anti-Rh ₀
rh	—	—	—
rh'	+	—	—
rh''	—	+	—
rh'rh''	+	+	—
Rh ₀	—	—	+
Rh ₁	+	—	+
Rh ₂	—	+	+
Rh ₁ Rh ₂	+	+	+

genic and therefore the most common cause of clinical complications. In fact, in most clinical laboratories, the tests are usually confined to the use of anti-Rh₀ serum alone. For clinical purposes, individuals of any of the four types, rh, rh', rh'', and rh'rh'' should be considered Rh negative (Rh₀ negative) because they can all be sensitized to the most important Rh factor, Rh₀. As blood donors for Rh-negative patients, however, only type rh (triple Rh negative) individuals should be used, in order to avoid reactions in patients sensitized against the rh' or rh'' factor.

As soon as I had demonstrated the existence of eight Rh blood types, it was obvious to me that I had to consider all possible modes of inheritance of the Rh blood types just as in the case of the A-B-O blood groups. With the product theorem, referred to above, I disproved the existence of separate genes for each of the Rh factors, and it was then evident that the eight Rh types are inherited by a series of multiple allelic genes. Eight principal Rh genes are recognized at the present time, which are designated as *r*, *r'*, *r''*, *rs*, *R₀*, *R₁*, *R₂*, and *R_z*, respectively. It will be noticed that, as in the case of the A-B-O groups and the M-N types, care has been taken to use different symbols for the genes and the agglutinogens in order to avoid ambiguity. The base letter "R" stands for the rhesus factor, and in this case the symbols for the genes are even simpler than the symbols

TABLE VIII—THE Rh PHENOTYPES AND GENOTYPES

Pheno- types	Genotypes
rh	<i>rr</i>
rh'	<i>r'r'</i> and <i>r'r</i>
rh''	<i>r''r''</i> and <i>r''r</i>
rh'rh''	<i>r'r''</i> , <i>rsr</i> , <i>rsr'</i> , <i>rsr''</i> , and <i>rsrs</i>
Rh ₀	<i>R₀R₀</i> and <i>R₀r</i>
Rh ₁	<i>R₁R₁</i> , <i>R₁r'</i> , <i>R₁r</i> , <i>R₁R₀</i> , and <i>R₀r'</i>
Rh ₂	<i>R₂R₂</i> , <i>R₂r''</i> , <i>R₂r</i> , <i>R₂R₀</i> , and <i>R₀r''</i>
Rh ₁ Rh ₂	<i>R₁R₂</i> , <i>R₁r''</i> , <i>R₂r'</i> , <i>R_zr</i> , <i>R_zr'</i> , <i>R_zr''</i> , <i>R_zry</i> , <i>R_zR₀</i> , <i>R_zR₁</i> , <i>R_zR₂</i> , <i>R_zR_z</i> , <i>R₀rs</i> , <i>R₁rs</i> , and <i>R₂rs</i>

for the agglutinogens, in contrast to the situation for the A-B-O groups and the M-N types.

As shown in Table VIII, 36 genotypes are theoretically possible corresponding to the 8 Rh phenotypes. The number of recognizable phenotypes has been increased to 27 types by the discovery of the so-called Hr antisera, of which three varieties exist corresponding to the three Rh antisera. The Rh and Hr antisera are reciprocally related like the M and N antisera, so that the reactions determined by the 8 Rh genes can be summarized as shown in Table IX. With the aid of this table, the phenotype corresponding to any given genotype can readily be deduced, but for the sake of brevity the details are not reproduced here.

For medicolegal use, most experts have available antiserum of specificity Rh₀, rh', rh'' and hr', and a few also have antiserum of the specificity hr''. Antiserum of specificity Hr₀ is still not available for general use. The medicolegal implications of the Rh-Hr tests, using the first five named serums, can be summarized in the following rules.

1. Factors Rh₀, rh', rh'', hr', and hr'' cannot appear in the blood of a child unless present in the blood of one or both parents.

2. Parents of types Rh₁Rh₁ and rh'rh'

TABLE IX—THE Rh SERIES OF ALLELIC GENES

<i>Genes</i>								
<i>Designations</i>	<i>Approximate frequencies among N.Y.C. whites (per cent)</i>	<i>Corresponding agglutinogens</i>	<i>Reactions with Rh serums</i>			<i>Reactions with Hr serums</i>		
			<i>Anti-Rho</i>	<i>Anti-rh'</i>	<i>Anti-rh''</i>	<i>Anti-Hr₀</i>	<i>Anti-hr'</i>	<i>Anti-hr''</i>
<i>r</i>	38.0	rh	—	—	—	+	+	+
<i>r'</i>	1.4	rh'	—	+	—	+	—	+
<i>r''</i>	0.5	rh''	—	—	+	+	+	—
<i>r_y</i>	.01	rh _y	—	+	+	+	—	—
<i>R₀</i>	3.2	Rh ₀	+	—	—	—	+	+
<i>R¹</i>	40.4	Rh ₁	+	+	—	—	—	+
<i>R²</i>	16.4	Rh ₂	+	—	+	—	+	—
<i>R_z</i>	0.1	Rh _z	+	+	+	—	—	—

cannot have children of types rh, Rh₀, Rh₂ or rh'', and parents of types rh, Rh₀, Rh₂ and rh'' cannot have children of types Rh₁Rh₁ or rh'rh'. Or, more simply, hr'-negative parents cannot have rh'-negative children, and rh'-negative parents cannot have hr'-negative children.

3. Parents of types Rh₂Rh₂ and rh''rh'' cannot have children of types rh, Rh₀, Rh₁, or rh', and parents of types rh, Rh₀, Rh₁, and rh' cannot have children of types Rh₂Rh₂ or rh''rh''. Or, more simply, hr''-negative parents cannot have rh''-negative children, and rh''-negative parents cannot have hr''-negative children. As may well be imagined, the discovery of the Rh-Hr blood types has resulted in a substantial increase in the chances of exclusion for a falsely accused man, namely, from 30 per cent to about 55 per cent.

During the past few years, the writer has accumulated a series of approximately 450 cases of disputed paternity in which complete tests were done for A-B-O, A₁A₂, M-N, and Rh-Hr, including the factors Rh₀, rh', rh'', and hr'; more recently it has been possible to add also tests for factor hr''. Among these cases there were 31 in which paternity was excluded by the Rh-Hr tests. Among the 31 cases there were 14 in which paternity was also excluded by the

A-B-O tests, or M-N tests, or both. Thus, in as many as 17 cases, it would not have been possible to exclude the falsely accused man were it not for the more recently discovered Rh-Hr tests.

Obviously, the potentialities of the subject are far from exhausted, and studies which are continuing at the present time all serve to confirm Landsteiner's concept of an individuality of human blood somewhat analogous to the individuality of fingerprints. For example, the situation in the Rh-Hr types is actually even more complicated, since variants of the Rh factor have been found, particularly of the factor rh'. Moreover, no mention has been made in this review of the agglutininogen P and its variants, or of other independent blood properties recently found by Race and his collaborators as well as by the present writer and his associates. While the complexities to the casual observer may appear more and more bewildering, to specialists in the field they become more and more fascinating. It seems apparent that a common plan underlies the entire complex superstructure, and one of the main purposes of future research should be to discover this basic plan and the function served by the existence of individual differences in human blood.

Appraisal of the Clinical Aspects of the Rh Factor

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My presentation will be limited to the appraisal of some of the clinical aspects as they affect hemolytic disease of the newborn or erythroblastosis foetalis. The data are not easy to evaluate or to compare. There is a considerable variability in hemolytic disease of the newborn and many of the milder cases may be overtreated. While there may be no substitute for clinical observation or judgment, in most cases of erythroblastosis foetalis, the laboratory facts are reliable and in most instances, have given us exact diagnostic information which has proved invaluable in treating the affected infants. There are a number of clinical findings in the newborn which make a diagnosis of erythroblastosis foetalis or hemolytic disease of the newborn, obvious to all. The signs of edema, jaundice, pallor and purpura, twitching, convulsions, and splenic and liver enlargements are all characteristic. All these symptoms and signs may be mild, moderate or severe. There may be a marked anemia with reticulocytosis and an increased number of nucleated red cells in the peripheral blood. However, the diagnosis, in at least half of the cases, can not be made too early on clinical grounds alone, and particularly with the mild cases, may not be made for several days or weeks. The diagnosis may be suspected at all times when the mother is found to be RH negative and prenatal tests reveal anti-RH antibodies in her serum. Many of the involved infants are not anemic at birth and appear altogether normal. Within several hours jaundice is detected, and some degree of anemia develops. In some of these babies the signs and symptoms develop very rapidly so that in 24 to 48 hours, the infant appears very listless, cries weakly, refuses feeding or vomits the little it takes. Overwhelming toxicity supervenes and in spite of all measures at this time the infant succumbs. This was the usual story before the days of prenatal RH testing. At the present time, the diagnosis should, in nearly all instances, be made or suspected before

the baby is born. Prenatal testing of the mother with antibody tests, if necessary, should be performed so that there will be no delay in carrying out the appropriate treatment. There are a number of instances when the tests are incorrectly performed. Regardless of previous errors in RH testing, or failure to detect antibodies in the mother, the diagnosis can be definitely established serologically in a few minutes.

In the past 18 months the use of Coombs' reagent has given us miraculous and dramatic support. With the use of this serum, negative tests have ruled out hemolytic disease of the newborn due to RH or HR sensitization while positive tests indicated the presence of the disease. When it is not known whether agglutinins found in the mother have been left over from a previous pregnancy or transfusion, a negative Coombs' test rules out involvement of the infant. On the other hand, the infant may have been erroneously typed RH negative because the cells have been blocked by the antibody transmitted from the mother. Under these circumstances a positive Coombs' test establishes the diagnosis without question. In our series every involved infant had a positive Coombs' test whether the mother had an agglutinin in saline or in albumin.

It might be mentioned at this time that, as yet, we have no good method in detecting A and B sensitivity in the infant. We must depend to a great extent on the hematological and clinical findings. The anti-A and anti-B titers at times may be helpful. In this group, however, the infants, usually first born, recover spontaneously. Some may require a single transfusion or an injection of A and B substance; rarely is the A and B sensitization severe.

The prognosis of erythroblastosis foetalis at the present time is not as difficult to make as it has been in the past, provided however the infant is born alive and in fair condition. With the proper treatment nearly all infants survive and recover dramatically. Most of the difficulty arises in

trying to predict the outcome in a particular pregnancy. A rising titer is indicative of an involved infant, but there are numerous exceptions to these findings. Even with vast experience, one can not be too sure how severely an infant will be involved and whether premature delivery is indicated. We have had a number of women who have been told they would not have infants which could survive because of their high antibody titer and their homozygous RH positive husbands. These women, nevertheless, have been delivered of infants, who, following replacement transfusions, survived and developed normally. On the other hand, there are a number of instances when mothers with relatively low titers have had infants severely involved or even still born. Although there is some correlation between the titer in the mother and the severity of the involvement of the infant, there is still much to be desired for accurate prediction.

It has been mentioned by several authors, that if a woman highly sensitized to the RH factor waits for several years, the anti-RH antibodies in her serum may decrease or disappear and following this her chances of having an infant which would survive would be better. In our experience there seems to be no basis for such advice. We have found that one year or more following delivery, the antibody titer in albumin remains fairly constant. We have had an exceptional example where a woman was delivered of her last child at the age of thirty-five. There had been no transfusions in the interim. At ninety-four years of age, blood examination revealed her to be RH negative and fairly potent anti-RH antibodies in albumin were demonstrable. I am sure that there must be numerous examples throughout the country of sensitized women whose antibodies persist for decades and all that is necessary to cause further stimulation is another pregnancy or a transfusion. It would therefore seem proper, that if further pregnancies are contemplated in sensitized women, not to advise delay.

A few years ago there was a great number of Cesarean sections performed on women who had involved infants. The indications were often not warranted, the results poor, occasionally with the loss of

both mother and baby. Now the pendulum has swung the other way in most clinics, because of the poor results previously obtained. We feel, however, that there is a certain group of mothers whose only chance of having an infant which might survive would be to deliver the infant somewhat prematurely by Cesarean section. In considering this procedure all factors must be weighed carefully to assure the survival of the infant following appropriate treatment. This group is comprised of women who have had a previous baby with erythroblastosis which was still-born, or did not survive the first few days of life. In these cases, undue conservatism leads to loss of another infant which may have been saved. The results are not good, but it is sometimes the only chance of having an infant that will survive.

The treatment of hemolytic disease of the newborn is most important. While there have been a number of people who have become interested in the hematological and serological findings for the diagnosis of this disease, there are relatively few who have devoted themselves to properly carrying out the indicated therapeutic procedures. In even such a large city as New York, there are only a few centers where the infants with erythroblastosis foetalis can be properly handled. It would seem much better for a number of pediatricians to learn the serological tests, and their interpretation and the technique of replacement transfusion, rather than have to depend on a laboratory report and then upon others to carry out the treatment. In many instances, babies in poor condition are transported for many miles because of lack of knowledge and training in home institutions.

For a severely involved infant who requires a replacement transfusion our routine is more or less as follows:

A complete blood count is done. The hemoglobin and red cell levels are important in order to calculate the amount of blood the infant should receive in excess of that which is withdrawn. The weight of the baby has to be known in order to estimate the total volume of blood. The blood used should be preferably fresh, or no more than 24 hours old. If not fresh, it should be warmed to 37°C. to avoid shocking the

infant. The baby should be kept warm throughout the entire procedure, with oxygen therapy if necessary. In some institutions like the Childrens' Hospital in Boston, the entire procedure is carried out in a specially built crib. Most of these infants are in very poor condition and extreme care must be used in handling them. Recently the General Electric Company has manufactured a special washable electric blanket bunting for us. This can be regulated to any temperature desired. It should soon be available for use in smaller hospitals where the hot water bottles and electric pads are not only inadequate but at times dangerous.

The treatment of choice for an infant with erythroblastosis is replacement or exchange transfusion. In the severely involved babies it is the only treatment at present which gives good results.

It is entirely possible that some infants which received a replacement transfusion may have survived with the ordinary methods of repeated transfusions, as in the past, but from our experience we have no way of determining which infants may suddenly begin to hemolyze blood rapidly, and by the third or fourth day succumb in spite of the fact that hemoglobin and red cells are fairly normal. It would therefore seem safer to do an exchange transfusion even in the borderline cases.

The technique of exchange transfusion is fairly simple. There are a number of techniques, such as replacement by way of the femoral vein, the radial artery and saphenous vein, and exchange by way of the umbilical vein. All appear to give equally satisfactory results. The question as to the superiority of one method over another will not be discussed at this time.

The exchange by the way of the umbilical vein has been the procedure of choice in practically all our replacements. It is thought by some that after the first 24 hours the umbilical vein can not be used, but we have been able to use this method as long as 68 hours after birth, without any ill affects. One should be prepared to use any method which seems suitable in a particular case. A special plastic catheter is passed into the umbilical vein and about $\frac{1}{2}$ to $\frac{1}{4}$ of the blood volume is removed

before any blood is replaced. The infant is kept on the anemic side until the procedure is more than half finished. In small infants a good portion of the plasma is removed from the donor's blood so that a smaller volume may be given in order not to overload the baby's circulation. We give 450 to 750 cc. of RH negative blood. Small amounts of calcium gluconate (1 cc.) are given a few times during the transfusion to counteract the rapid withdrawal of the available calcium. No heparin is used. After the exchange the infant is placed in a Davidson bed with oxygen if necessary. A large dose of vitamin K is given and repeated in 12 hours, 25,000 units of penicillin, B.I.D. for three days, and clyses are given, if necessary.

When possible we endeavor to leave the infant with an adequate red cell volume containing less than 5 per cent of its own cells. These remaining RH positive cells can be handled by the infant without danger whether hemolysis be slow or rapid. The Coombs' reagent is the only accurate method of determining how efficient the replacement has been. The antibodies transferred from the mother remain for 3 to 6 weeks at the end of which time RH positive cells can again be demonstrated in the circulation. However, at this time, the Coombs' test is negative.

The donor's blood is gradually eliminated from the baby's circulation and if there are any anti-RH antibodies remaining up to the fourth or fifth week, all the positive cells formed up to this time are destroyed so that some of the infants may require only a simple transfusion. By the sixth to eighth week increased production of red cells begins with moderate reticulocytosis. By the ninth to tenth week the trend is definitely upward and by the third month the infant approaches the normal figures for this age period and from then on develops normally. In a small percentage of infants mental retardation is noted and signs of kernicterus are found. The condition occurs in only a small percentage of patients and the pathogenesis remains quite obscure in spite of many theories. There are a few other complications of the disease which time does not permit me to discuss.

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ACADEMY OF MEDICINE

CONTENTS

Advances in Treatment of Malignant Disease . . . 271
C. P. Rhoads

Results of Operations for Hyperparathyroidism . . 285
William Barclay Parsons

The Therapeutic Role of Procaine and its Derivatives 298
E. A. Rovenstine and E. M. Papper

Treatment of Bell's and other Palsies 307
William Bierman

Recent Advances in the Domain of the Anti-Histamine
Substances: The Phenothiazine Derivatives . . 323
B. N. Halpern

Library Notes:

Recent Accessions to the Library 331

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MAILON ASHFORD, *Editor*

Published Monthly by THE NEW YORK ACADEMY OF MEDICINE
2 East 103 Street, New York 29, N. Y.

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE



MAY 1949

ADVANCES IN TREATMENT OF
MALIGNANT DISEASE

*The Ludwig Kast Lecture**

C. P. RHOADS

Director Memorial Hospital Center for Cancer and Allied Diseases. Professor of Pathology,
Cornell University Medical College, and Director of Sloan-Kettering Institute

THE search for chemicals to control cancer has followed a course much like the one pursued over the years by those who wished to transmute the elements. Every age has had its alchemists and every one its cancer remedy. The confidence of the credulous has been so repeatedly betrayed that it has recoiled from the repeated failures. A long series of bitter disappointments has led to a conditioned reflex: the view that all who search for new means of cancer control are idyllic dreamers, blissfully unaware of the impossibility of ever attaining their goal. In spite of alchemists and sceptics, however, transmutation is now a fact. Similarly, notwithstanding past failures, mistakes, and confusion, progress in cancer therapy now is being made. It is as yet an enormously ill-defined, vague, stirring and struggling of an amorphous mass of scientific facts, yet its tendency to take form and to move toward a definite goal is now both apparent and real.

The status of the struggle at present is seriously complicated, how-

* Presented October 4, 1948 before the 21st Graduate Fortnight of The New York Academy of Medicine.

ever, by recent observations¹⁻⁴ which, though they were not capable of confirmation, nevertheless indicated an important line of research. The study concerned a vitamin, a derivative of folic acid, scientifically known as pteroyl-gamma-glutamyl-gamma-glutamylglutamic acid, named by its manufacturer, teropterin. This play, though erroneous, was an enormously important development, since it has greatly aided definition of the true goal and possibly the means for attaining it. The folic acid story began with cancer, has gone through a long series of plots and counterplots, and now, in completely new form, with an O. Henry twist, is back on cancer again.

CLAIMS FOR FOLIC ACID IN THE THERAPY OF CANCER

Beginning in 1939 there appeared a series of papers by Lewisohn, Leuchtenberger, and their associates, in which they described the ability of a number of different materials to cause the disappearance of spontaneous mammary tumors in female Rockland Farm strain mice. Certain of these materials, notably a spleen extract⁵ and a barley extract,⁶ were said to cure about 30 per cent of the treated animals. A similar rate of regression in untreated controls was not observed.

A yeast extract⁷ was also described as effective, and efforts were undertaken to isolate its active principle in pure form. Inositol⁸ was the only one of the crystalline vitamins of the B complex present in yeast which was alleged to be effective in inhibiting the experimental tumor.

The vitamin, pteroylglutamic acid (folic acid) was first described by Snell and Peterson⁹ as a growth factor required by certain bacteria. Shortly afterward, Pollack, Taylor and Williams,¹⁰ at the University of Texas, in assaying B complex vitamins in various tissues found the highest level in certain animal neoplasms.

In 1944, Lewisohn, et al.¹¹ reported that injections of a crude extract which had many of the properties of folic acid would inhibit in mice the growth of a transplanted sarcoma. A year later¹² they described cures of spontaneous breast cancers in three different strains of mice treated by daily intravenous injections of the same material. Subsequently, they stated that the same activity was shown by pteroyltriglutamic acid, a conjugate of folic acid, and that pteroylglutamic acid (folic acid) itself was without any value when tested under similar conditions.¹³ This statement was remarkable since good evidence exists to prove that all the folic acid conjugates are broken down in mammals to simple folic

acid. This is indicated by the disappearance of all signs of deficiency of the vitamin and the recovery of folic acid from the urine of animals given the conjugates.

The development of synthetic procedures next made available in quantity, and in pure form, pteroylglutamic acid (folic acid), pteroyldiglutamic acid (diophterin), pteroyltriglutamic acid (terophterin), pteroylheptaglutamic acid (vitamin B₉ conjugate).

Sugiura,¹⁴ using material similar to that employed by Lewisohn, was unable to confirm the latter's observations. Rhoads¹⁵ also failed in later experiments.

Lewisohn believed that the conditions observed in his laboratory had not been followed exactly by the groups which failed to obtain like results. Particular reference was made to the importance of daily injection of the material intravenously and by no other route, of preventing its inactivation by light, and of making open biopsies of the neoplasms. In general, those who tried to confirm the claims did their best to observe the conditions originally described, but in many instances differences of technique crept in. Later, however, Lewisohn reported that he could duplicate his results by feeding the pteroyltriglutamic acid (terophterin) and that injections were not required. The experiments of Rhoads were done without open biopsy since that procedure was found to result frequently in surgical cure of the soft, localized neoplasm unless precautions were observed.

While the work of Lewisohn was in progress, and during the war, an apparently wholly unrelated activity developed under the secrecy of the army research program on chemical warfare. A group of agents known as the nitrogen mustards, or B-chlorethyl amines, was found to have a profoundly toxic effect on both normal and neoplastic tissue of the hematopoietic system. Gilman and Philips¹⁶ and Jacobson,¹⁷ were leaders in this extraordinarily interesting enterprise. For the past four years an extensive program of distribution and of reporting on the effectiveness of the best of these compounds, HN₂ or methyl-bis (B-chlorethyl) amine, has been in progress under the National Research Council. Karnofsky,¹⁸ who had this activity in charge, has recently reported. The summary of his report is so clear and unequivocal that I quote it here.

"Nitrogen mustard represents a new and valuable agent for the management of inoperable neoplastic disease. Methyl-bis (B-chloro-

ethyl) amine hydrochloride (HN_2), the nitrogen mustard in clinical use, is a systemically acting cell poison most closely related in its therapeutic effects to total body irradiation. Its advantages over total body irradiation are that it is less expensive, easier to administer, its toxic and therapeutic effects develop more quickly, tissue recovery is more rapid and its dosage can be more safely controlled so that maximum therapeutic doses are possible. Total body irradiation causes less nausea and vomiting, and its therapeutic effects may be more prolonged.

" HN_2 is an effective, temporary, palliative agent of irregular activity in Hodgkins' disease, lymphosarcoma, chronic leukemia, polycythemia vera, mycosis fungoides, primary lung carcinoma and, to a much lesser degree, in other miscellaneous neoplastic disorders. There is little evidence, however, that it alters the course of these diseases or appreciably prolongs life. Its great value is as an adjuvant to x-ray therapy in the palliation of neoplastic disease. X-ray therapy is more effective in treating localized disease. . . . HN_2 should be given only when definite indications exist. Because of its toxicity and unpleasant side-effects, its indiscriminate trial in patients with inoperable cancer or in terminal stage of the disease is entirely unjustified."

Studies of the mechanisms by which nitrogen mustard exerts its transient but perceptible effect upon some neoplastic tissues led to three interesting findings. The material was very active in arresting mitosis, a process which is the duplication of structures rich in nucleic acid. Exposure to nitrogen mustard of material such as *Drosophila* (fruit fly) or *Neurospora* (the mold), suitable for the study of genetic effects, revealed promptly that the chemical was very effective in causing mutations. This suggested, because of the prominence of nucleic acid in the structure of chromosomes upon which mutations depend, that the poison affects nucleic acid or some mechanism concerned with its production. Finally, it was learned that nitrogen mustard, in exceedingly low concentrations, inhibits the normal synthesis of cellular nucleic acid.

These findings, that the growth of certain neoplastic cells can be adversely influenced by a compound, nitrogen mustard, which interferes coincidentally with cellular structures containing nucleic acid and enzymes for forming them, were of great interest. They suggested that there might be found other tumor-inhibiting agents among those which inhibit nucleic acid metabolism.

The next development came in observations based, it is stated, upon a critical analysis of the data of the Lewisohn group. Farber and his associates¹ reported studies of ninety patients with malignant disease. Both pteroyldiglutamic acid (diapterin) and pteroyltriglutamic acid (teropterin) were used in an effort to establish the therapeutic value of these compounds in treatment. No evidence of toxicity was found, and improvement in energy, appetite, and sense of well-being was noted. It was believed that this could be ascribed in many—but not all—instances, to a psychological effect only; to the improved morale resulting from institution of a potentially-useful therapeutic procedure. In a few instances, diminution of pain also was reported.

It was stated in the report that in a few cases a causal relationship was apparent between the administration of the glutamic acid compound employed and objective evidence of change in the patient's condition or the histological appearance of the tumor.

In a larger group of patients in which conventional therapeutic agents, such as irradiation therapy, were also employed, changes were observed under conditions which suggested that it was the addition of the glutamic compound (teropterin) which played an important part in their appearance. As examples of these changes, reference was made to temporary decrease in the size of subcutaneous nodules of an amelanotic carcinoma, temporary decrease in the size of metastases to the lung from a carcinoma of the testis, two instances of necrosis seen on pathological examination of tumors, and two drops in acid phosphatase level in one patient with carcinoma of the prostate gland.

Farber concluded that further investigation of pteroyltriglutamic acid (teropterin) was justified from the data obtained. The implication is clear that the authors felt that a real therapeutic effect had been exerted irregularly on the course of the neoplasms subjected to study.

Somewhat later, in a symposium conducted by the New York Academy of Sciences, Klainer² described improvement in a patient with metastatic carcinoma of the breast treated with pteroyltriglutamic acid (teropterin) and also given testosterone. Lehy and his associates³ reported the results of the administration of pteroyltriglutamic acid (teropterin) to twenty patients with cancer. Relief of pain and sense of well-being were reported, but there were no objective changes in the lesions.

Meyer,⁴ in a paper given at this same symposium, reported

subjective and objective improvement in 12 patients with neoplasms of the hematopoietic system treated with pteroyltriglutamic acid (teropterin).

Simultaneously, in the same communication, and concerning the same types of neoplasms, Meyer reported beneficial results of exactly the same, or pteroyltriglutamic acid (teropterin) induced type, brought about by two compounds which function wholly as antagonists, or neutralizers, of pteroylglutamic acid (folic acid). These are also presumably antagonists of pteroyltriglutamic acid (teropterin), since that compound functions as folic acid in the mammal and is converted to that compound.

In the same symposium Woll¹⁹ reported that Rous sarcoma of chicks could be prevented by maintaining the birds on a diet free of folic acid by administering three folic acid antagonists, 4-amino folic, 4-amino folic with d(-)glutamic and 4-amino pteroylaspartic acid. Furthermore, once the tumor had developed, the antagonists would prevent further growth.

Thus in a noteworthy symposium, both folic acid and its antagonists were advocated simultaneously for the control of cancer, an anomaly which aroused widespread attention.

Earlier, Spies,²⁰ Davis,²¹ Doan²² and, later, Lawrence,²³ all reported their failures to influence neoplasms of hematopoietic tissue in any way with pteroylmonoglutamic acid (folic acid).

Following these reports, both pteroyldiglutamic acid (diapterin) and pteroyltriglutamic acid (teropterin) were distributed by the manufacturer to at least 225 investigators. These were then circularized by letter to ascertain the results they obtained by the use of the compounds. Their reports are recapitulated in a report of the Council on Pharmacy and Chemistry of the American Medical Association.²⁴ The summary states that the facts available from this questionnaire do *not* yet support the view that pteroyltriglutamic acid (teropterin) has an anti-cancer effect. The method employed to assess the value of the preparation is criticized.

It is the considered opinion of many that the subjective relief referred to by some of those who answered the questionnaire could have been entirely the response to suggestion. This sort of response has been reported for many years in countless studies of inert material administered to patients with cancer.

THERAPY OF NEOPLASMS BY ANTAGONISTS OF FOLIC ACID

The important role of folic acid in hematopoiesis was first demonstrated by Spies²⁵ for macrocytic anemia and by Darby and Jones²⁶ for sprue. Their observations were rapidly and amply confirmed. They were in accord with the fact that, in animals, the induction of a folic acid deficiency by withholding that compound from the diet results in anemia and leukopenia.

The principle of anti-metabolite effect first established by Woods²⁷ for the sulfonamides and extended by Woolley²⁸ suggested an interesting possibility for the induction of a folic acid deficiency. This would require the preparation of compounds so similar to folic acid that the cells would take them up as folic acid but at the same time so dissimilar that they could not function as folic acid in cellular life.

The first antagonist to folic acid was d(−)methyl folic acid synthesized by Martin and his associates.²⁹ Its effect was demonstrated by its ability to inhibit the growth of *S. fecalis* R and the fact that pteroylglutamic acid (folic acid) would overcome this inhibition.

In 1947 Franklin, Stokstad, and Jukes³⁰ described the acceleration of a pteroylglutamic acid deficiency in mice and chicks by a crude chemical antagonist. The active component of the crude preparation may be 7-methyl-pteroylglutamic (L) acid. Slow growth, anemia and leukopenia were caused and pteroylglutamic acid (folic acid) prevented the appearance of the syndrome. In 1948 the same authors³¹ reported the toxic effects of feeding a new antagonist prepared in pure form, 4-amino-pteroylglutamic acid (aminopterin), to mice. This material had previously been shown to act as a folic acid antagonist in inhibiting the growth of *S. fecalis* R since the effect was reversed by increasing the level of pteroylglutamic acid in the medium. In the experimental mice, some depression of blood values as a sign of folic acid deficiency was effected by the 4-amino-pteroylglutamic acid (aminopterin), but although reversal of the toxic effect by pteroylglutamic acid (folic acid) was observed at certain levels of dosage, this could not be demonstrated at higher levels.

The next development was the report by Farber and his co-workers³² of temporary remissions induced in acute leukemia in children. These remissions followed the use of the folic acid antagonist, 4-amino-pteroylglutamic acid (aminopterin). It is of interest that the

term "antagonist" was used, even though in mice the toxic effect of this compound could only be reversed by the administration of folic acid within a very narrow range of dosage.

In his communication, Farber reports an "acceleration phenomenon" in the leukemic process seen in the marrow and viscera of his children with acute leukemia treated by the injection of the folic acid conjugates, pteroyldiglutamic acid (dioppterin) and pteroyltriglutamic acid (teroppterin). This is not referred to in his original publication¹ on the use of these materials in the treatment of patients with neoplastic disease.

Since the disease was accelerated or made worse by folic acid, and since other leukotoxic agents, such as the nitrogen mustards, have a harmful effect upon the pathologic leukocytes of leukemia, as well as upon normal ones, and since a folic acid deficiency inhibits leukocyte formation, a trial of the therapeutic value of a deficiency induced by folic acid antagonists was undertaken.

Studies on fourteen children with acute leukemia treated with the folic acid inhibitor, pteroylaspartic acid, and seven treated with methyl pteronic acid are referred to, but it is stated that the results will be reported in another publication.

Sixteen children with acute leukemia were given the 4-amino-pteroylglutamic acid (aminopterin). Of these sixteen, ten were reported as showing clinical, hematological, and pathological evidence of improvement of an important nature of three months' duration at the time of the publication. Six showed no response. Of the ten patients who were favorably affected, five are reported on in detail and it is stated that the courses of the others were essentially similar. Distinct improvement, well-sustained, clearly followed the administration of aminopterin to these five children. It should be noted, however, that of the five cases reported, two showed spontaneous remissions without treatment, and two of the remissions which followed treatment were not wholly complete.

In a later communication Heinle and Welch³³ described rapid hematologic relapse following the administration of pteroylglutamic acid (folic acid) to three patients with chronic leukemia. They reasoned, like Farber, that since pteroylglutamic acid (folic acid) made them worse, a deficiency of it should make them better. An effort to induce a deficiency of pteroylglutamic acid (folic acid) in one of these pa-

tients by a diet low in its content of that substance, combined with the administration of a crude antagonist and an intestinal bacteriostatic, was followed by a drop in the leukocyte count and the death of the patient.

The most recent published statement on this subject is an editorial in the journal *Blood*.³⁴ This investigator reports the occurrence of 4 remissions in his series of 16 adults with acute and sub-acute leukemia treated with 4-amino-pteroylglutamic acid (aminopterin). He speaks of a "distinct improvement" of the marrow picture, a rise in red cells and platelets and also refers without detail to one remission in a case of leukemia in childhood. The statement is made that the factor of spontaneous remission can be completely ruled out in his own and in Farber's series of cases.

Farber³² mentions the stomatitis which can be a serious toxic complication of the use of 4-amino-pteroylglutamic acid (aminopterin). The *Blood* editorial also refers to personal communications from various centers where that drug and related materials are being used. They indicate, it is said, that the results have often been disappointing, and that adverse reactions such as hemorrhage or aplastic anemia are common.

In any discussion of the results of the use of a potentially active therapeutic compound in the treatment of leukemia, either in adults or in childhood, a precise definition of the term "remission" is required. Furthermore, careful comparison of the results should be made with the course of the disease in a like number of untreated patients of similar types. It is not proper, in the opinion of many, to apply the term "remission" to a simple decrease in the number of pathological leukocytes in the circulating blood, even though this be associated with some decrease in the number of blast forms, but not their disappearance, and with evidence of decrease, but not absence, of other manifestations of the disease. Rather, perhaps "improvements" should be the word applied to incomplete trends toward health.

Fluctuations are known to be a feature of untreated leukemia, even the acute disease. Transfusions, required so frequently, are probably a contributing factor here since they are often followed by profound symptomatic response.

The term "remission" properly should be reserved for an essentially complete restoration of normal hematologic function and health

in all other respects. It is not applied to a simple leukotoxic effect, such as can be exerted by a number of agents, without essentially complete disappearance of all manifestation of disease. As mentioned previously in the five patients whose records were reported by Farber,³² two showed periods of spontaneous remission while untreated, and in two the remission was incomplete as far as is indicated by the data presented.

In a series of seven children with acute leukemia treated by Burchenal³⁵ at the Memorial Hospital, two showed remissions, which could be ascribed to the folic acid antagonist used in therapy. In the remaining patients, in no instance did more than a transient and partial improvement of blood levels result from aminopterin therapy. Furthermore, toxic effects were distinct with a tendency to hemorrhage and evidence of gastro-intestinal irritation.

To establish clearly, then, the role of anti-folic therapy of acute leukemia in children is very difficult at the present time. Several workers have presented evidence that it is of value in inducing remissions irregularly but sufficiently often to be a matter of very great interest and importance. More data are urgently required.

Studies of the effect of the administration of folic antagonists, principally 4-amino-pteroylglutamic acid (aminopterin), have been made by Burchenal³⁵ in an extensive series of adults with myeloid leukemia, and a few patients with other neoplasms of the hematopoietic system. In chronic myeloid leukemia, a leukotoxic effect with a drop in leukocyte count to more normal levels can be exerted regularly. This is not infrequently associated with a decrease in size of involved organs but rarely with a subsequent restoration of full erythropoietic activity. In general, however, these salutary results are not seen unless the drug is pushed to the point of distinct and possibly serious toxicity. The periods of improvement which follow are usually not complete remissions, though these do occur.

Aminopterin is an experimental drug of great interest. In man, however, except possibly in acute leukemia in children, there is little differential between its effect on neoplastic compared with normal cells. That it has an injurious action on the leukocytes of leukemia is a fact beyond question, but more data will be required before we can conclude that it will regularly restore the patients to health.

Tests have been made at the Memorial Hospital, Sloan-Kettering Institute, in very great detail on the effect of folic acid antagonists on

the course of neoplasms in animals. These tests reveal that great care must be used in setting up the experiments and in evaluating the results. Certain cardinal points must be borne in mind. The first is that results must be expressed in terms of a ratio between the primary toxicity of the compound employed and the inhibition of tumor growth effected. It is not enough simply to state that one compound is less or more toxic than another. The second principle is that a spectrum of different tumors of varying sensitivity must be employed in testing, since there is very considerable variation in their response to growth-inhibiting agents. Finally, response of the tumor in terms of cytological injury must be compared with that of the tissue in the body most sensitive to inhibition of growth, notably the lymphatic tissue and the bone marrow. The desired end in all such experiments is to establish clearly a preferential injurious effect on the neoplastic, as compared with any normal, cell.

If these criteria be applied to the use of aminopterin in animals, as its effects have been observed in an elaborate and extensive series of studies, the fact is apparent that, as in man, the agent has a profound leukotoxic effect, but not a strong differential or preferential toxicity for neoplastic over normal cells. Partial regressions of certain sensitive experimental tumors of mice and rats can be obtained by the administration of aminopterin in doses sufficiently near the tolerated level so that some of the animals are killed by the therapeutic agent. If a dose level is maintained which can be tolerated by the animals without fatality for a period of seven days, it is extremely difficult to establish clearly any profound inhibitory effect of the compound on tumor growth, and certainly none which is not associated with evidence of bone marrow injury. Similar results have been attained in limited experiments on patients.

In experimental animals the use of the 4-amino-N¹⁰-methyl pteroylglutamic acid (α -methopterin)³⁶ is associated with more definite evidence of a restraining effect upon the growth of neoplastic tissue. With this compound, both in experimental leukemia in mice and in transplanted sarcoma 180, a well-defined inhibition of growth of the neoplastic cells can be demonstrated at dose levels which are well under those which are tolerated by the animals. There is a suggestion, furthermore, that in human beings some objective evidence of growth restraint of sensitive neoplasms can be obtained, although much further

data will be required before any final conclusion is justified.

The experience of Memorial Hospital, Sloan-Kettering Institute, with aminopterin and a-methopterin can be summed up with the statement that the first compound seems to have little preferential injurious effect on neoplastic, compared with sensitive normal, cells. The second, however, seems to exert some preferential injurious action on certain types of sensitive neoplasms.

The work presented is one of the most interesting studies now under way in the pathologic physiology of neoplasms. It is of no great moment today whether this or that compound has perceptible—or more than perceptible—effects on leukemia. It is of very great moment, however, that in the field of compounds which may well interfere with the formation or metabolism of nucleic acid, substances are at hand which poison certain neoplastic cells, even though this effect be a weak one.

A mass of studies indicate that the cancer cell in general contains more nucleic acid than does its normal analogue. The agents which cause cancer are those which induce mutations by their effects on nucleic acid-containing structures, the chromosomes. Certain viruses, and other self-reproducing agents capable of exerting profound effects upon the nature of cells, are nucleic acid in nature. What would be more reasonable than to find that the fundamental difference between normal and neoplastic cells resides in the nucleic acid of which the templates for our bodily manufacture of cellular material is composed. And if this difference is there to be found it is quite likely to be done by the demonstration of a differential effect of a nucleic acid precursor on normal, as compared with cancer, cells as by any analytical method. Studies of this type compose, indeed, the procedure of empiric analysis through differential inhibitions, by which many great discoveries have been made.

Great honor is due those who, step by step, have battered out the links in the long chain of discoveries which have bound cancer research with fundamental aspects of nutritional biochemistry. How surprised would Miescher be, were he alive in this, his 104th year, to learn that his isolation of nucleic acid from fish sperm and its characterization would be the first step toward a better understanding of the cancer cell.

It is apparent from the studies which have been made that no millennium in cancer chemotherapy has been attained by the use of any

anti-folic material so far described. Nor, indeed, is any generally useful agent yet at hand. It is equally apparent, however, that a most important field for investigation has been opened up to study. With the great variety of analogues of folic acid and related compounds which can be prepared synthetically in the laboratory and the reliable methods of assay available, it may be hoped that materials showing a greater preferential toxic effect to neoplastic cells will be obtained in the future.

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RESULTS OF OPERATIONS FOR
HYPERPARATHYROIDISM*

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THE first operative cure of generalized osteitis cystica fibrosa by removal of a parathyroid adenoma was reported by Mandl¹ in 1925, just under a quarter of a century ago. Since then, and mostly in the past 15 years, several hundred cases have been operated upon with success and many articles have been written discussing the physiological principles involved, the differential diagnosis and operative technique. Norris² two years ago in a review of the literature found 254 operated cases, which he included in his interesting article that deals largely with the embryology of the parathyroid glands.

It seemed to us that it might interest you to have a summary of the 32 cases operated on at the Presbyterian Hospital. A few of these have been reported previously,^{3,4} and some were operated on by Hanford, Elliott and Self, who have kindly allowed me the privilege of including their cases with my own.

Inasmuch as prognosis is the main thing of interest to the patient after relief from symptoms has been achieved, our cases will be presented to you including the follow-up results, which bear a distinct relation to the stage of development of the disease at the time of operation. No disease entity can be subjected to a rigid classification, but it is useful in considering hyperparathyroidism to keep in mind its two important ill effects, namely, skeletal deformity and particularly renal damage. Operation prior to the inception of either of these will have a brilliant result. Operation after either has occurred will not eliminate bony deformity nor will it affect renal damage that has become irreversible. This fact re-emphasizes the value of early diagnosis, and the vital importance of considering the possibility of hyperparathyroidism being present when any of its symptoms are noted that

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TABLE I—NO RENAL IMPAIRMENT. NO CALCULI

Case	Sex	Age	Duration	Symptoms	Ante-Op.			Site	Size	Wt. (kgs, avg)	Tel-ang	Follow-Up
					Ca.	P.	Ptase					
F.G. 608926	F	43	1 yr.	G.I. Pain, Polyuria Wt. loss,	12.9	1.7	84.4	L.U.M.	5.2 x 1.2 x 1.9	4.0	0	Kyphosis, O.K. 8 yrs.
L.D. 897066	F	44	3½ yrs.	Back pain, Fatigue, Nervous,	12.1	2.1	49.0	L.L.	3.3 x 2.0 x 0.8	3.65	+	O.K. 1 yr.
*A.B. 742846	F	21	5 mos.	Pains,	14.5	2.3	37.0	L.L.	4.0 x 3.5	+	+	O.K. 3¾ yrs.
*E.D. 737265	F	41	1 yr.	Polyuria Fracture, G.I. Pain,	17.4	2.6	10.8	L.L.	4.0 x 5.0	27.0	Ca. 4.9 +	Bowing femora, O.K. 4½ yrs.
K.B. 802801	M	44	1½ yrs.	Polyuria G.I. Fatigue,	13.6	2.8	8.1	L.U.M.	2.2 x 1.9 x 1.2	0	0	Asymptomatic, T 9 compressed, O.K. 1 yr.
***L.L. 439199	F	53	?	Paget's, Diag. on Chem.	11.8	2.3	35.8	L.U.	2.5 x 1.5 x 1.1	0	0	Paget's progressing, Ca. 9.6 at 12 yrs.
B.N. 480103	F	63	5 yrs.	Pains, Weak. Deformity,	12.8	1.9	11.6	L.U.M.	2.2 x 1.2 x 0.5	Ca. 6.6 +	Ca.	Deformed but walking and works at 10½ yrs.
**R.L.M. 766057	F	29	3 yrs.	Pain. Weak.	13.2	2.1	23.3	L.U.	3.2 x 1.8 x 1.5	4.0	+	Caesarean at 1 yr. O.K. 3 yrs.
F.D. 428858	F	76	? yrs.	Vague G.I. Fatigue	15.1	2.7	12.3	R.L.	5.0 x 3.2 x 1.5	12.0	+	O.K. 12 yrs.

*Operator: J. M. Hamford.

**Operator: R. H. E. Elliott.

***Previously reported (B).

cannot be adequately explained on another basis. Such complaints as lassitude and fatigue, polyuria, indigestion, as well as vague muscle and bone pains may be present for months before a spontaneous fracture or bony swelling occurs, and of course all cases of renal colic should be immediately suspect.

Our 32 cases fall into four main clinical groups with calculus formation, or calcification within the kidney substance, with or without renal damage, as the significant elements. Bony deformity is naturally of great importance to the patient but is not important clinically as far as postoperative restitution of normal physiological calcium and phosphorus balance is concerned. One group of nine patients had neither calcium deposition nor renal impairment, twelve presented calculi, or a history of having passed one or more stones, or renal calcification without any definite impairment of renal function, whereas eleven could be classified as showing renal damage. Of these eleven, five were borderline, with high normal nitrogen retention and low normal P.S.P. excretion rate, the other six presented evidence of serious renal insufficiency. It is interesting to note that all but one of this group of eleven with renal damage had well marked deposition of calcium either within the kidney or as frank urinary calculi. Thus, out of the entire group of 32 individuals there were 22 (68 per cent) who came in with a history of having passed one or more calculi, had renal or ureteral calculi present, or showed definite x-ray evidence of calcification within the kidney substance.

The follow-up results at intervals from a few months to twelve years bear out the thesis that renal function at the time of operation determines the prognosis as to life expectancy. Moreover, all cases showed an immediate return to normal calcium and phosphorus levels, except after the second operation on one case of recurrent carcinoma and one of multiple tumors. There was no immediate operative mortality, but five patients died later of renal insufficiency and one died of recurrent functioning carcinoma of the parathyroid. Table I, which includes those with good renal function and no calculi, is of interest in that all but three complained of pains of a more or less vague type before deformity or fractures appeared. One of these (K.B.) has an asymptomatic compression of T 9; another (L.L.) in whom hyperparathyroidism was discovered in the course of frequent blood studies, has had Pager's disease of long standing,³ and the third

TABLE II—RENAL CALCULI WITHOUT DEFINITE RENAL IMPAIRMENT

Case	Sex Age	Duration	Symptoms	Ante-Op.			Site	Size	Wt. Gms.	Tet- any	Follow-Up
				Ca.	P.	P'tase					
****M.B. 521397	F 55	13 yrs.	Small stone.					3.0 x			
			Repeated	12.8	1.9	2.7	U.M.	1.2 x		0	Cripple but O.K. at 10 yrs.
			fractures.					0.5			
D.G. 546806	F 50	7 yrs.	Weak. 1 stone.					4.0 x		Ca.	
			Polyuria.	11.2	2.7	30.3	L.L.	3.0 x	11.0	5.5	O.K. at 9 yrs.
			Emotional.					1.5		+	
A.W. 532131	M 35	17 yrs.	Bilateral	13.0	1.2	3.8	I.U.	1.9 x		?	Gout. O.K. at 9 yrs.
			calculi.					0.8 x	0.5		
								0.4			
**R.M. 750663	F 32	2 yrs.	Weak.					2.5 x		+	Chvostek 3 yrs. with normal
			Nervous.	12.4	2.4	24.0	I.L.	1.5 x		+	Ca.
			1 stone.					1.3			Hypertension with preg. at 3½ O.K. at 4 yrs.
B.S. 567000	M 56	10 yrs.	Calculi.					4.5 x		Ca.	Carcinoma.
			Pain.	18.6	3.2	33.9	I.L.	4.5 x		5.9	Chem. O.K. 18 mos.
			Weakness.					3.2		+	Recurred.
B.S. (2 yrs. later)	58	6 mos.	Pain.	19.1	3.1	23.0	2 ant. neck.	1.5		0	Post-op. Ca up.
			Wt. loss.					diam.			Down-hill course.
			Polyuria.								D. 5 yrs. after 1st op.

Table II—(Continued on next page)

Table II—(Continued from preceding page)

N.I., 735037	F 38	1½ yrs.	Pain. G.I. Wt. loss, 20 lbs.	15.9	2.2	15.2	1.	2.6 x 2.5 x 1.7	5.9	+	3 ops. for calculi. O.K. at 9½ yrs.
N.M., 868500	F 42	3 yrs.	Fractures, Weak. Colic.	17.9	3.0	5.1		1.8 x 4.0 x 1.5	4.7	0	Ops. for calculi—bowing femur. O.K. 1½ yrs.
E.R., 662891	F 50	14 mos.	Calculi, Weak. Pains.	12.9	3.3	3.8	L.U.	1.7 x 0.6 x 0.3	0.16	0	O.K. 1 yr.
***F.E., 682482	F 45	3 yrs.	Pains. Wt. loss. Passed calculi.	15.8	2.3	31.2	L.U.M.	3.0 x 2.3 x 1.3	7.0	Ca. 5.6 +	No residual calc. O.K. 6 yrs.
***R.L., 672708	M 37	6 yrs.	Bilateral calculi.	12.3	2.0	3.5	L.L.	2.2 x 1.5 x 0.9		+	Renal colic. O.K. 5½ yrs.
**W.S., 811995	M 27	3 yrs.	G.I. Weak. Calculi. Fracture.	18.0	2.5	6.2	L.S.	3.0 x 2.3 x 1.8	5.2	+	Ops.: Femur; papillary thyroid carcinoma. O.K. 2 yrs.
O.L., 583499	M 40	4 yrs.	Pyuria. Renal colic.	11.1	1.4	10.1	R.L.	2.5 x 2.0 x 1.2		+	O.K. 9 yrs. Pyuria.

**Operator: R. H. E. Elliott.

***Operator: E. B. Saff.

****Previously reported (3).

TABLE III—BORDERLINE RENAL DAMAGE

Case	Sex Age	Dura- tion	Symptoms	Ante-Op.			Site	Size	Wt. Gms.	Tet- any	Follow-Up
				Ca.	P.	Plase					
F.C. 874519	F 49	9 mos.	Colic. G.I. Scoliosis. Fracture.	14.8	3.3	28.1	R.L.	4.0 x 2.5 x 2.0	6.5	+	Continuing pyuria. Chem. O.K. at 1½ yrs.
****A.G. 782704	F 55	8 yrs.	Nephrectomy. Wt. loss. Colic. Pains.	13.4	1.4	25.0	R.L.	4.0 x 2.5 x 1.1		+	Carcinoma rectum, op. 10 yrs. O.K. at 12 yrs.
***R.E. 684467	M 29	10 yrs.	42 calculi passed. Several ops.	11.8	2.4	2.9	L.S.	1.5 x 0.9 x 0.4	0.45	+	O.K. at 1½ yrs.
A.N. 650235	F 53	11 yrs.	Multiple calculi.	12.6	3.0	3.1	R.L.	1.8 x 0.8 x 0.6		0	Several ops. for calc. O.K. at 6½ yrs.
***T.C. 713533	F 50	2 yrs.	Fractures. Bone pain. Nephritis.	10.6	2.0	43.1	L.U.M.	3.5 x 3.0 x 1.3	13.0	0	No post-op. tetany. Ca 6.4 O.K. at 5 yrs.

***Operator: E. B. Self.

****Previously reported (3).

(F.D.) was diagnosed during studies for supposed cholelithiasis. All of these patients are living with normal blood calcium levels at intervals from one to twelve years, in some cases with deformity but even so with improved general body function.

In Table II are listed those with calcium deposition but without renal damage. In this group there are two cases worthy of particular attention. Patient M.B. had been almost bed-fast for ten years because of her marked deformities due to repeated spontaneous fractures. She is still crippled ten years later but is not in pain and has suffered no renal impairment. Another patient in this group (B.S.) died five years after his first operation and three years after his second for carcinoma of the parathyroid. He had a large tumor with characteristic blood chemistry and x-rays; showed postoperative tetany with a drop of his serum Ca to 5.9 and did excellently for eighteen months. He returned after six months of pain and weight-loss, again with hypercalcemia and an elevated phosphatase. At the second operation two tumors were found in the muscle layers which were considered as possibly implants seeded at the time of the first procedure. No other tumors were found but metastasis must have occurred as no improvement in blood calcium level followed operation and his course was steadily down-hill, in spite of radiotherapy, to his death three years later.

Table III lists five patients with calculi and borderline renal impairment. In these individuals nitrogen retention was at the upper limits of normal and P.S.P. excretion rate was at low normal levels. Unquestionably, at some date these patients might have developed serious renal damage, but it is interesting to note the long duration of symptoms in this group, namely, 2, 8, 9, 10 and 11 years. One of them was a young man aged twenty-nine, who had passed forty-two calculi, but the others were around fifty years of age and it is not clear why their kidneys stood up so well. One of them (A.G.) who was reported in 1938³ had an abdominoperineal resection of the rectum in 1946 and is still doing well in spite of the fact that she lost one kidney many years ago and has a calculus in the remaining kidney. Patient A.N. has had several operations for ureteral stone but is doing well nearly seven years after operation. In none of our cases has there been any suggestion of solution of calculi following the restoration of a normal blood calcium level. New stones have not been formed, apparently, but those already present have remained unchanged.

TABLE IV.—WELL MARKED RENAL DAMAGE

Case	Sex Age	Duration	Symptoms	Aute-Op.			Site	Size	Wt. Gms.	Tel- ang	Followe-Up
				Cn.	P.	P'ase					
***M.W. 345901	F 52	15 yrs.	G.I. Calc. Kyphosis.	13.0	6.0	20.0	R.L.	3.0 x 2.0 x 0.8	4.5	+	O.K. at 2 yrs. Rising N.P.N. D. at 4 yrs.
***C.G. 384613	M 34	2 yrs.	Polyuria. G.I. Weak. Fracture.	15.4	2.5	31.8	R.L.	2.7 x 1.6 x 1.0	3.5	+	Renal calcific. O.K. at 4½ yrs. Rapid uræmia. D.
M.S. 432444	F 50	1½ yrs.	G.I. Colic.	13.0	2.9	4.4	R.S.	1.6 x 1.0 x 0.4	0.71	0	Progressive renal insuff. High B.P. D. 2 yrs.
***M.R. 423516	F 44	11 yrs.	Renal calc. Nephrectomy.	14.9	6.5	16.7	R.L.	4.5 x 3.8 x 2.2	17.0	+	Same as above. D. 18 mos.
***H.K. 713224	F 36	2 yrs.	Pains. Fracture.	14.1	3.1	7.6	L.U.M.	4.5 x 4.0 x 2.5	36.0	0	Renal calcific. Rising N.P.N. and B. P. at 5 yrs.
F.G. 832349	M 28	2 yrs.	Nephritis. Fractures.	14.2	2.5	12.9	L.	Sev. small.	0	0	O.K. 22 mos. Pain. Polyuria.
F.G. (2 yrs. later)	30	2 mos.	No calc. Weakness. Polyuria	12.1	5.5	23.5	R.U.	2.7 x 1.5 x 1.7	3.06	+	Renal insuff. increasing at 6 mos.

***Operator: E. B. Self.

****Previously reported (4).

Table IV contains the data on the patients with serious impairment of renal function. All of these except E. G. had renal calculi or calcification. In one patient (C.G.) there was massive calcification throughout a horseshoe kidney.⁴ He exhibited moderate nitrogen retention, his P.S.P. excretion was satisfactory, but he showed constant albuminuria and low specific gravity. He did excellently for a period of four years and then began to show hypertension and rising nitrogen retention. Six months later he was admitted in uremia and made a rapid exitus. At postmortem all the remaining parathyroids which had been apparently normal at operation now showed typical secondary hyperplasia. His kidney showed extreme arterio- and arteriolar sclerosis, renal atrophy, and extensive calcification largely in the tubular area. Here and there were relatively normal glomeruli, so his renal failure was definitely on a quantitative as well as qualitative basis.

Two of the patients in this group gave long histories, one of eleven and one of fifteen years' duration, but the others had noted symptoms for two years or less. One of these (E.G.) was the only patient to present multiple small adenomata. His history began with discharge from the Navy because of nephritis. Later he suffered spontaneous fractures of the femur and patella and had one fruitless exploration of his neck at another hospital. Being unsatisfied with some small suspicious nodules behind the left lobe, we split his sternum and removed the tissue in the thymic area. Four small adenomas about 0.5 cm. in diameter were found in the specimen. On this admission he showed a B.U.N. of 24, a P.S.P. excretion rate of 20 per cent, and concentration to 1.011. He exhibited postoperative tetany and for a year and a half showed marked improvement in general well-being, with blood chemistry normal and definite recalcification in his skeleton. For 3 months before his second admission he noted weakness and polyuria and a rising blood calcium was found. At the second operation a tumor measuring 2.7 x 1.5 x 1.7 cm. and weighing 3.065 gms. was found embedded in the right lobe. On this admission his B.U.N. had risen to 90, his P.S.P. excretion was only 10 per cent and his concentration was only to 1.010. No suggestion of carcinoma was found, the tumor being a characteristic arrangement largely of rose red cells. He showed moderate tetany postoperatively; his calcium eventually falling to 9.6; but his strength has not improved; he looks badly and at 6 months is exhibiting progressive renal insufficiency from which

TABLE V.—ALL 32 CASES

<i>Cases</i>	<i>Renal Damage</i>	<i>Calc.</i>	<i>Good F.U.</i>	<i>Living Ill</i>	<i>Died Later</i>	<i>Normal Chem. Balance</i>	
						<i>Temporary</i>	<i>1-12 Yrs.</i>
9	0	0	9				9
12	0	+	11		1	1	11
5	?	+	5				5
5	+	+		1	4		5
1	+	0			1	1	

34 Operations, Mortality 0.

22 Calculi or Calcification—68%

Excellent Results 1-12 Yrs. in Re. Blood Chemistry—93%

Temporary—100%

he will eventually die. Since writing the above, a letter has been received from his doctor to the effect that pains are increasing and that x-rays show further progression of his disease but no data on blood chemistry or renal function are available. The clinical problem in his case is: Has he one or more other functioning tumors; is he developing secondary hyperparathyroidism; and, in view of his serious renal situation, can we offer him anything by another search of his neck? Our experience with secondary hyperparathyroidism due to severe renal insufficiency is completely discouraging. I am sure we must re-admit him for evaluation as to the possibility of re-operation, discouraging as the outlook may be. Fortunately, the occurrence of multiple adenomata is as rare as diffuse primary hyperplasia but both do occur and require early diagnosis, perhaps more vitally even than in cases of a single adenoma. The problem at operation is also far more difficult as the tumors may be extremely small and may be scattered about. In this particular case a small tumor had been removed at the first operation from near the site where the larger tumor was discovered two years later embedded in the thyroid. Probably it was so small two years previously that it was not discovered, being embedded in a sulcus of the thyroid.*

* On the day after this paper was presented a letter was received stating that E.A. had died two days previously without post mortem examination.

As another example of severe renal insufficiency, patient M. R. had lost one kidney and at the time of operation had an N.P.N. of 75 with P.S.P. excretion of 7.5 and ++++ albuminuria. She died 18 months later of progressive renal disease. Obviously the results in this group are disappointing but most of them had several years of relative comfort, which makes the operation worth while even in the face of grave renal disease. With the exception of E.G., hypercalcemia did not reappear in any case in this group.

Table V summarizes these 32 cases. Note that 32 cases are summarized whereas there were 34 operations. The two instances of a temporary return to normal chemical balance were in B. S., the patient with recurrent functioning carcinoma of the parathyroid who died of cancer and hyperparathyroidism, and E. G., the one patient with multiple adenomata, who was discussed in the last paragraph.

In addition to the above 32 cases of hyperfunctioning proved adenomata, we operated on one case of Milkman's syndrome, being at the time ignorant of the condition, and explored two cases of advanced renal disease with osteoporosis. At autopsy during this period of fourteen years three non-functioning oxyphile tumors were discovered, and two non-functioning parathyroid carcinomas were operated on by L. W. Sloan. In one the tumor suggested a carcinoma of the thyroid, in the other the tumor formed part of a cystic intrathoracic goitre. Both of these patients have died of other causes in no way connected with their parathyroid tumors.

There is no point in indulging in a complete statistical study of this series. Suffice it to say that our age and sex incidence is in accord with that quoted by Norris.² Our cases added to his, make it an even thing between right and left side as the site of the tumor. Seven of our tumors (namely 21.8 per cent) were in the upper mediastinum, but we have split the sternum in only one case, as the other upper mediastinal tumors could be reached and removed from above. However as our series grows it is probable that this procedure will have to be done more frequently.

The articles by Churchill and Cope⁵ and by Cope⁶ discuss the pathology and the surgical technique so adequately that there is no point in dwelling on these points other than to re-emphasize the necessity of exploring both sides to determine the total parathyroid equipment present. If a tumor is not readily found, the tracheo-

esophageal groove on both sides, the area behind the esophagus, and the upper mediastinum should be explored before resorting to splitting the sternum. In the article by Norris² 84 per cent of tumors were of the lower parathyroid, namely, the gland arising from the anlage in the third branchial pouch. The gland normally occupying the upper position in the adult grows from an anlage in the fourth pouch. In the third pouch is the anlage for the thymus and the lower parathyroid. As the thymus grows downward this parathyroid migrates with it and may go all the way to the depths of the anterior mediastinum or be dropped anywhere along the route, usually of course, stopping near the inferior thyroid artery from which it gets its blood supply. Cope⁶ has pointed out that one can often find an atypically placed adenoma by following an anomalous branch of one of the thyroid arteries. In any case the surgeon must remember this embryological migration in planning his search in the neck, and the posterior as well as the anterior mediastinum.

The postoperative therapy has two objectives; first to maintain an adequate urinary output and, secondly, to control postoperative tetany. Oliguria or even temporary anuria may occur after operation, possibly because of the sudden shift in calcium excretion due to the drop in circulating calcium, which follows the sudden change in circulating hormones as calcium now moves back into the osseous system. There may be difficulty in taking enough water by mouth in the first 48 hours, so an intake of 3,000 cc. should be arranged for by supplementing the oral intake with intravenous fluid. Not over 1,000 cc. of dextrose in saline should be given in order to avoid NaCl retention, therefore, the major portion of the intravenous solution should be dextrose in water. In patients with severe decalcification a marked drop occurs in the circulating calcium well into the tetany level, in fact, one of our patients showed a drop to 4.9 mg. per cent. Therefore, such patients can be expected to exhibit a well-marked tetany and should be started on a prophylactic anti-tetany regime before tetany appears. The postoperative orders should include 5-10 gms. of calcium gluconate in the infusion fluid, and 2 cc. of parathormone to be given in the late afternoon. This regime is continued until the patient can take enough extra milk and cheese to provide the required amount of calcium. If tetany does supervene, AT 10, hytakerol, should be started after a few days to allow the parathormone

to be discontinued a week later. The administration of calcium must not be overdone, and only small amounts if any of viosterol should be given to avoid renal deposition of calcium. Usually the calcium level will be normal in at the most two or three weeks. After a month or two there will be no need for using AT 10 provided a normal blood calcium level has been present for a few weeks. Those with minimal decalcification may not exhibit any signs of tetany and will not require any treatment, so one can safely wait until tingling or a Chvostek sign appears before starting therapy. In our thirty-two cases there were twelve instances in which no symptoms of tetany appeared and therefore no treatment was required.

Hyperparathyroidism due to an overfunctioning adenoma of a parathyroid gland is a well-marked clinical entity that is curable by operation, as is shown by restitution of normal levels of calcium and phosphorus in the circulating blood that seem to be permanent, or at any rate persist as normal for years. If untreated the results are marked skeletal deformity and invalidism due to pain and weakness, with eventual death due to renal insufficiency. Diagnosis and operation prior to deformity and renal damage will prevent the appearance of these sequelae. It cannot be stressed too strongly that this condition be kept in mind in patients, even without renal calculi or obvious skeletal deformity, whenever any of the early symptoms characteristic of this condition are present and are not adequately explained on another basis. Only thus will earlier diagnosis be made, insuring an excellent result by avoiding the serious complications that otherwise are inevitable.

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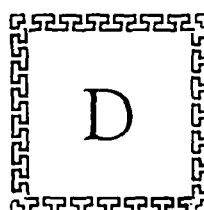
THE THERAPEUTIC ROLE OF PROCAINE AND ITS DERIVATIVES *

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 DURING THE 43 years that have elapsed since Einhorn announced the synthesis of p-amino-benzoyl-diethylamino-ethanol, the drug now known as procaine, it has become fully established as the most popular agent for local, regional and spinal anesthesia. Any drug with such wide usage is necessarily the object of many laboratory and clinical experiments designed to determine conclusively its pharmacological properties, its toxicity and to define its optimum use clinically. That the desired goal of such researches has not been achieved is now obvious from the considerable new material being added to our knowledge of procaine in the very recent past and at the present time. The most significant of these later experiments in both the laboratory and clinic are associated with the use of procaine administered intravenously.

Procaine was injected first into the veins of man 40 years ago.¹ This was done with a tourniquet in place and its object was to produce anesthesia of the extremities. The practice was soon abandoned. The present widespread use of intravenous procaine is a recent addition to therapy. It is readily understandable why intravenous procaine was so long avoided. Standard textbooks and other medical literature repeatedly pointed out the real danger of delirium, convulsions and death following the injection of procaine directly into the vascular system under any circumstances. There were numerous reports describing fatal convulsions in man after comparatively small amounts of procaine were inadvertently injected intravenously.

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Given October 12, 1948 before the 21st Graduate Fortnight of The New York Academy of Medicine.

In our laboratories (1940) procaine was given intravenously to anesthetized dogs during experiments undertaken to determine a means for protection against cardiac arrhythmias produced by injecting epinephrine.^{2,3} A definite protection was demonstrated and later similar results were observed in humans. This was substantiated during the war by Burstein when an opportunity was afforded for more extensive and better controlled observations in a busy army thoracic surgery center.⁴ The administration of intravenous procaine in large amounts in the anesthetized patient was followed by successful attempts to use the drug therapeutically in unanesthetized individuals.^{5, 6, 7}

It is now determined from extensive clinical observation that comparatively large amounts of procaine can be tolerated by man when given slowly by vein. With this knowledge intravenous procaine has been "tried" as a therapeutic agent for a surprisingly large number of unrelated clinical conditions. It has been used as an analgesic, for vasodilatation, to relieve muscle spasm, to diminish cardiac irritability and for an anti-histamine effect.

CLINICAL APPLICATION

The empirical application of intravenous procaine in clinical medicine has gained momentum without a well-defined fundamental basis for its action. This circumstance has occasioned a wide discrepancy in the reported results from its use. There is much speculation concerning the precise mechanism or mechanisms to explain the effects observed when the drug is administered as a therapeutic agent.

The essential action of procaine has been described as a direct one on the arterioles and capillaries with widespread dilatation. Although there is clinical evidence that peripheral circulatory dilatation occurs, conclusive experimental support in humans is lacking. Direct measurements of surface temperature should show an increase if capillaries in the skin are dilated. Our own efforts to establish this in man have given negative results. Dilatation probably could be produced if a large enough amount of procaine could be given intravenously. The serious toxic reactions to such doses constitute a barrier.

Graubard, Robertazzi and Peterson⁸ gave procaine intravenously to relieve the muscle spasm of poliomyelitis. They were optimistic with the results and others have made similar observations. No explanation for this effect has been established.

There is ample clinical evidence that cardiac irritability is reduced with procaine applied topically to the myocardium or given intravenously.^{2, 9} This effect is firmly established and is in accord with theoretical considerations in that there is a similarity in chemical configuration with quinidine, benadryl and other compounds which act as protoplasmic depressants upon the myocardium.

The anti-histamine action of procaine is not established by laboratory investigation although it has been successfully used to treat serum sickness.¹⁰ This has been attributed to an anti-acetylcholine action. Harvey¹¹ has shown that procaine depresses the response of the terminal efferent fibers to acetylcholine and decreases production of acetylcholine at these sites. Conduction in nerve fibers may depend to some extent upon release and removal of acetylcholine, a process which is inhibited by the neutralizing action of procaine.

The reported analgesic effect of procaine given intravenously has provoked considerable speculation as to the mechanism involved. It has been suggested that it follows the leakage of procaine into the perivascular areas to reach the nerve endings through damaged capillaries. This can not be accepted until analysis of fluids at the site of injury are made. It was further suggested that analgesia may be the result of central action. This is supported by experiments on changes in pain threshold using the Hardy-Wolff-Goodell technique. Bigelow and Harrison,¹² using subcutaneous injections found a rise in pain threshold of about $\frac{1}{3}$ of normal or the same range with therapeutic doses of acetylsalicylic acid. Using the drug intravenously, similar determinations were made here.¹³ It follows that the clinical results reported are not consistent with the elevations of pain threshold observed. Either the concept of pain threshold is not so important in the evaluation of an analgesic drug, or the therapeutic benefits are the result of some other process.

In the wide use of procaine intravenously, more consistent agreement on its effectiveness has been demonstrated in the control of pain following trauma. There is general agreement that patients with fractures and other musculo-skeletal injuries experience less pain when procaine is administered.⁸ In these groups are those with surgical trauma. Although this use of procaine has been established, it should be pointed out that pain syndromes of this nature have a wide individual variation and constitute a clinical group extremely difficult to evaluate in deter-

mining the effectiveness of analgesics. This is true also of the patients with pain from inflammatory reactions. In the latter group, optimistic results are reported in treating pain in the arthritides, neuritides and vascular disease. Considerable evidence has accumulated to warrant the use of intravenous procaine for burns, pruritus, and allergic skin reactions. Intravenous procaine has been used as an analgesic during parturition and for minor surgical procedures. One may say conservatively now that procaine may be an analgesic of consequence for patients with pain associated with trauma and inflammation. The favorable clinical application in other pain circumstances has not been established to the extent that it surpasses other means for effective therapy.

The evidence accumulated on the ability of procaine to correct alterations of cardiac rhythm is sufficient to establish it as the present drug of choice. This statement is qualified for the anesthetized patient only, since the amount needed in patients without the protection of anesthesia is too toxic for clinical usage. During anesthesia, procaine is of questioned prophylactic value, but finds its indication in the reversal of an abnormal rhythm. This should be further qualified to include the ventricular arrhythmias only. It is the firm conviction here that this latter use of procaine is more effectively accomplished when a single dose is given rapidly at the time its need is obvious. The aim is to provide the heart with an effective dose for a brief time during which irregularities of rhythm may be abolished.

TECHNIQUES

In efforts to determine the amount of procaine to produce maximum analgesia and other therapeutic effects, various recommendations have been made. In this regard there are two goals: to establish analgesia and to avoid aggravating or serious toxic reactions. Graubard and his associates⁸ suggested a "procaine unit" calculated at 4 mgm./Kg. of body weight to be given in 0.1 per cent solution in isotonic saline in 20 minutes. Such calculations would be more accurate if obesity were not a factor and if they were determined by an accurate analysis of the rate of destruction of the drug. It is true that this calculated dose is tolerated without toxic manifestations and this may follow the fact that its destruction occurs in plasma at a rate almost as rapid as it is being administered. The clinical impression from the experience here is that effective intravenous procaine medication can be had by an amount

of the drug that continuously provides mild toxic manifestations. These include such symptoms as apprehension, metallic taste, slight nausea, vertigo and a feeling of warmth. If more serious symptoms of muscle tremors, delirium and convulsions are produced, the drug must be discontinued to avoid failure of the circulation and respiration.

Procaine may be administered to unanesthetized patients in 0.2 per cent solution for rapid effect and to avoid large amounts of fluid if this is desirable. The rate that it should be given is widely variable with individuals and must be determined with the criteria of effective analgesia in the light of mild toxic manifestations as a guide.

The most favorable effects in the treatment of arrhythmias in the anesthetized individual have followed the rapid injection of 100 mgm. of the 1.0 per cent solution.

Vitamin C is often given with intravenous procaine and many clinicians use the barbiturates for their prophylaxis against toxic reactions.

MECHANISM OF ACTION

Notwithstanding this vast accumulation of clinical experience with intravenous procaine, the mechanism of action, distribution in the tissues and its precise fate is still undetermined. It would seem that this fundamental knowledge should be available before the precise role of procaine in therapy can be determined accurately. Consequently a systematic study of the pharmacology of procaine has been undertaken in our laboratories. More detailed reports of these studies are available elsewhere but essentially the initial effort was to devise chemical methods for the identification of procaine and the products of its hydrolysis.¹⁴ With these methods it was learned that an enzyme present in plasma was largely responsible for the almost instantaneous destruction of procaine to its metabolites, di-ethyl-amino-ethanol and para-amino-benzoic acid. In addition to establishing the manner of disposition of procaine in vivo, it was desirable to determine whether the observed toxic effects were associated with procaine itself or some product of its normal degradation. It seemed entirely possible that the therapeutic action of procaine could be exerted by a metabolite which was less toxic than the parent drug or if this were not the case, that procaine itself could be altered by chemical substitution in the molecule to make a more stable and effective drug.

In studies upon normal man, Brodie and his coworkers¹⁴ demon-

strated that procaine is very rapidly hydrolyzed after intravenous administration and that urinary excretion is almost negligible as a method of disposition of the injected drug. Since 70 to 95 per cent of the para-amino-benzoic acid (free and conjugated) in procaine is recovered in the urine, it was apparent that this material was largely unaltered in the body. On the other hand, amounts of di-ethyl-amino-ethanol equivalent to 20 to 35 per cent of the original procaine can be isolated from the urine. When para-amino-benzoic acid and di-ethyl-amino-ethanol are injected as such, quantitative recovery in the urine is identical with that described when these substances are administered in the esterified form as procaine. It is evident, therefore, that the di-ethyl-amino-ethanol product of the hydrolysis of procaine is further metabolized *in vivo* in a manner as yet undetermined.

The fact that the concentration of procaine in the plasma does not increase with continuous intravenous administration while that of the alcohol metabolite does, as clinical effects are noted, suggests that the latter may be the pharmacologically active agent rather than the parent drug. The role of para-amino-benzoic acid has not been completely investigated, but the previously known behavior of this substance and the results of some few experiments offers little support for the possibility that it exerts many of the actions commonly attributed to procaine.

It seemed desirable, therefore, to investigate the pharmacological effects of di-ethyl-amino-ethanol upon man and laboratory animals. Observations early in the course of these studies indicated that the toxic effects were qualitatively similar to procaine, but large doses could be given intravenously before these were apparent. The margin of safety was significantly greater than with procaine. The relative lack of toxicity of this material and its greater flexibility with regard to dosage, pointed the way to a comparison with the orthodox actions of procaine. Comparisons were directed toward the properties which have been reported for procaine.

DI-ETHYL-AMINO-ETHANOL STUDIES

Among the early efforts to compare the effects of the alcohol metabolite of procaine with the parent drug were those directed toward its ability to diminish cardiac irritability. This action which may be due to a protoplasmic depression of conductivity in cardiac muscle has been

studied in anesthetized animals and unanesthetized man: Di-ethyl-amino-ethanol is somewhat more efficient than procaine, although in larger doses, in reversing cyclopropane-epinephrine ventricular arrhythmias in the dog to sinus rhythm. The therapeutic benefit of the alcohol persists for longer periods than that produced by procaine. In unanesthetized humans the experience to date, although not extensive or conclusive, suggests that ventricular arrhythmias may be suppressed often when comparatively large doses of the alcohol (0.5 to 5.0 gms.) are given rapidly by vein. In another report, Rosenberg and his associates¹⁵ describe 14 patients with ventricular extrasystole 13 of whom had normal rhythm after receiving di-ethyl-amino-alcohol. Another 8 patients with ventricular tachycardia were similarly treated with a restoration of pre-existing rhythm following in 6 of them. This effect on the specific tissues of the heart varies in duration. Similar results were unobtainable when attempts were made to treat supraventricular arrhythmias.

Di-ethyl-amino-ethanol has local anesthetic properties. Using local intracutaneous injections it was determined that the drug produced definite anesthesia for 20 to 30 minutes when a 10 per cent concentration was employed. No anesthesia was obtained when weaker solutions (1.0 per cent) were used.

The effects of di-ethyl-amino-ethanol upon the pain threshold were studied by a modified Hardy-Wolff-Goodell technique. Four grams of the drug given rapidly produced a definite, although slight, elevation of threshold. This elevation was within the range to be had with therapeutic doses of acetyl-salicylic acid and is inconsistent with clinical observations as is true with similar studies with procaine.

Skin temperature determinations were made before and after di-ethyl-amino-ethanol was given intravenously to determine vasodilatation in the skin and its actions upon smooth muscle. Amounts of 3.0 to 4.0 grams regularly produced an increase in skin temperatures of 3 to 9°C.¹⁶ This definite effect was not repeated here with non-toxic amounts of procaine and suggests the alcohol more effective than the ester in overcoming vascular spasm.

The systemic analgesic effects of di-ethyl-amino-ethanol are similar to those that may be anticipated from intravenous procaine. The opportunities to complete significant studies have not been available during the short period the drug has been under observation. The early impression is that di-ethyl-amino-ethanol in relatively large doses is equally

efficient with procaine as an analgesic. It has the advantage of less troublesome administration and almost none of the toxic manifestations.

When toxic reactions from di-ethyl-amino-ethanol were observed they followed rapid injections of large amounts of the drug. These were similar to the mild reactions from procaine and are transient. Vertigo, slurred speech, a feeling of warmth, nausea and mild retching have occurred. Mild hypotension of short duration has also been determined. It is safe to say, however, that the serious toxic effects from procaine are not a hazard when its metabolite, di-ethyl-amino-ethanol is used therapeutically.

SUMMARY

Intravenous procaine is now popular therapy for many unrelated clinical conditions. It is used for analgesia, for vasodilatation, to depress cardiac irritability and for an anti-histamine effect. The mechanisms for this variety of activities are unknown. Some of those suggested are discussed.

The technique for administering procaine intravenously is suggested.

One of the metabolites of procaine, di-ethyl-amino-ethanol has been used experimentally and clinically as a substitute for the parent drug. The results presently obtained from these studies are outlined.

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TABLE I—CHRONAXIES OF PATIENT MAKING EARLY RECOVERY

Frontalis17	Risorius16
Corrugator16	Orbic. Oris Lower09
Orbic. Oculi10	Orbic. Oris Upper15
Zygomaticus24	Triangularis16
Quad. Labii Sup.34	Mentalis24
Procerus14	Quad. Labii Inf.20

A case of Bell's Palsy of 13 days duration. Complete recovery in three weeks.

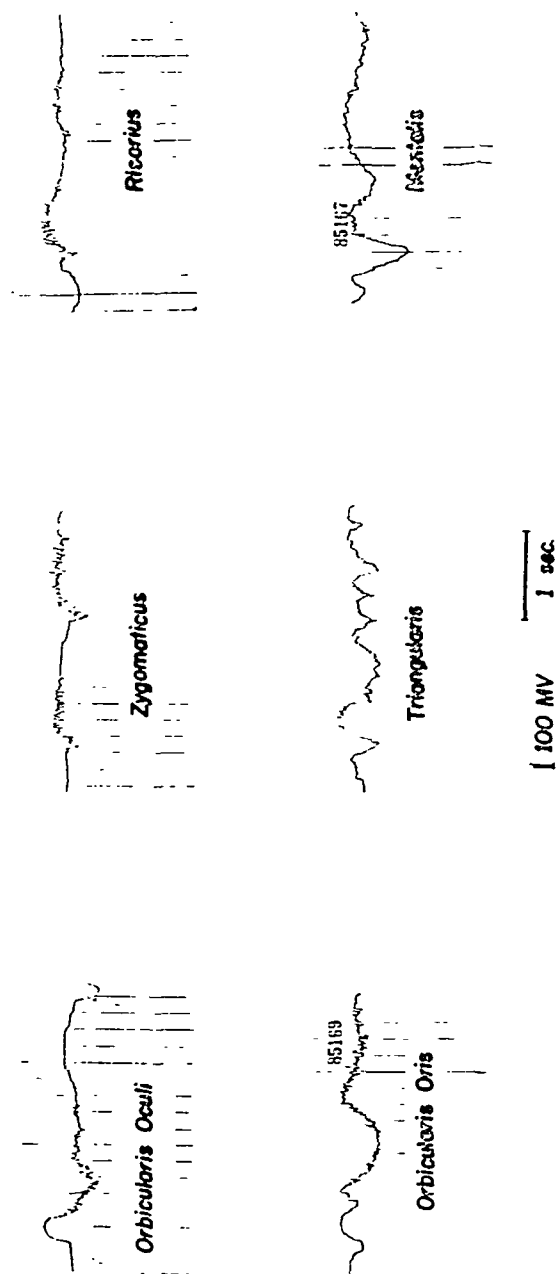
TABLE II—PROGRESSIVE CHRONAXIES OF PATIENT MAKING LONG DELAYED RECOVERY

	6/9	8/6	12/17	3/18	6/11
Frontalis30	4.0	.20	.11	
Corrugator20	4.0	.23	.17	
Orbic. Oculi	1.6	2.4	.30	.40	
Quad. Labii Sup.	1.0	2.3	.40	.60	
Procerus30	3.0	.44	.38	
Orbic. Oris Upper	1.0	2.0	3.4	2.0	.40
Orbic. Oris Lower	1.0	5.0	4.0	1.3	1.2
Mentalis	1.7	4.8	2.4	2.7	2.0
Quad. Labii Inf.	4.2	2.0	5.0	1.0	.80

myography.³ Denervated muscles may show abnormal or completely absent potentials. On the other hand, intact neuromotor mechanisms can be detected by observation of small normal potentials even when voluntary movement be not discerned. Both of these diagnostic procedures also have prognostic value.

The absence of a voluntary motion can be due to difficulties other than damage to a motor nerve. Thus, the limitation of motion may be caused by a condition of hypertonus in the antagonists. For example, the inability to extend the leg may be due to overactivity of the hamstrings, rather than to weakness of the quadriceps.⁴ Another possible factor is incoördination. The voluntary impulse is not directed to the desired muscle, but to some other which may indeed be the antagonist. A third factor appears to be due to the difficulty in formulating the concept of a motion after a period of inactivity. The occasionally observed rapid restoration of motion following directly upon the con-

ELECTROMYOGRAMS OF APPARENTLY IMMOBILE MUSCLES



No voluntary motion visible, yet electromyograms indicated contractions of muscle fibres.

Figure 1

traction of a muscle by electrical stimulation might be explained on this basis—of the reinauguration of the pattern of the motion. A fourth factor is the presence of atrophic changes in muscles, bones, arthritic and periarthritic tissues. These changes may occur not only as a result of neural damage but also because of long periods of immobilization following injury or disease of skeletal structures. Under these circumstances motion becomes limited and painful. The patient follows the line of least resistance and desists from further attempts at mobilization. A fifth factor is the failure to recognize the possibility of motion even when the organic mechanisms for such activities are present. An injury or a disease may have made motion inadvisable or impossible for a period of time. With the passing of such temporary disability, the patient may continue in the belief that he cannot move the extremity. Correct medical advice or an intense emotional stimulus may then account for what would appear to be a “miraculous cure.” At times the physician may be responsible for such a fallacious point of view—as illustrated by the patient with hemiplegia, the onset of which had occurred four months previously. She had been cautioned not to get out of bed because of her supposed inability to stand on her feet. A detailed functional examination revealed that the muscles of her involved lower extremities had adequate power to permit her to stand and to walk at first with assistance and shortly thereafter by herself. One or more of these factors may coexist in an extremity with a true paralysis of one or more muscles.

Much can be accomplished by skillfully guided exercises. Exercises are termed “passive” when the operator performs the entire movement and “active” when the motion is carried out by the patient himself.⁵ There are three types of active exercises—which are referred to as “free,” “assistive” and “resistive.” When free movements are to be performed the influence of gravity should be reduced as much as possible to minimize resistance. This may be accomplished by immersion of the part in water (as in tanks and pools), by slings, or with smooth boards whose surfaces are powdered to diminish friction. Assistive movements are performed actively by the patient, aided by the operator or by gravity or by some outside force, for example, a weight and pulley. Their object is to permit the patient to accomplish more than he could unassisted. Resistive exercises are made more severe by the resistance offered by the operator, by gravity, or by weights and

POLIOMYELITIS

ELECTROMYOGRAM FROM PAIR QUADRICEPS

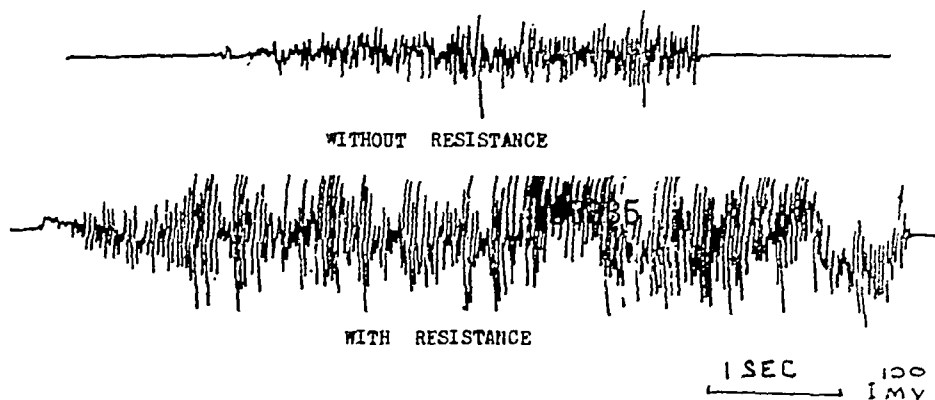


Figure 2A

POLIOMYELITIS

ELECTROMYOGRAM FROM PAIR QUADRICEPS

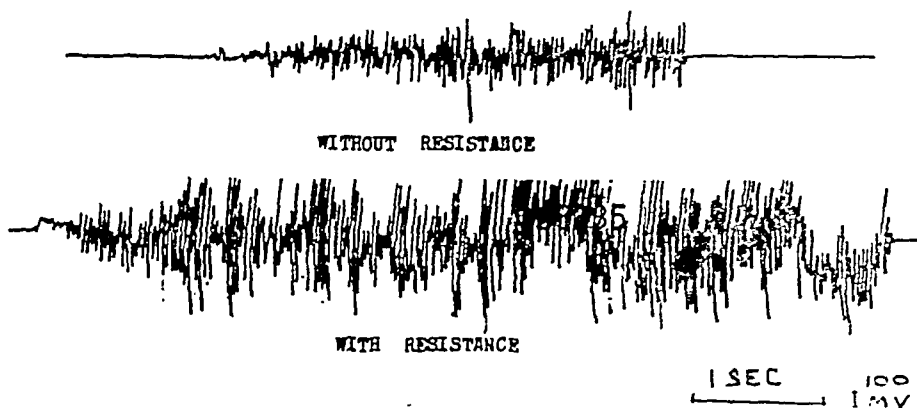


Figure 2B

apparatus. Effective exercises depend in large measure upon the motivation of the patient. He must realize that a desire to improve is essential and that such improvement depends upon his willingness to expend considerable muscular effort. When such correct motivation does not exist, psychologic as well as physical treatment is necessary. Of late, the emphasis has been placed on the use of resistive exercises as soon and as vigorously as possible.⁶ Such emphasis appears valid as determined

by both clinical results and by electromyographic studies. These studies show that the use of resistance causes a marked rise in electromyographic potentials. This is due to the contraction of an additional number of muscle fibers.

In treatment of hypertonus, exercises are said to be made more effectual by the preliminary administration of certain drugs such as curare,⁷ prostigmine,⁸ or intravenous procaine.⁹ The administration of exercise is based on an evaluation of the status of muscles as determined by functional, electrical and electromyographic testing. The scope of functional testing has been enlarged to include the examination of the patient's ability to perform the activities of every day existence. The integration of functional abilities with the movements required in the performance of vocational activities has made many an individual who would otherwise be completely dependent, into a self-respecting, completely or partially self-sustaining member of society.

Physical medicine is important because it can exert a favorable influence on the trophism of the structures whose normal well-being is dependent on intact neural mechanisms. Regeneration of nerves can occur—axis cylinders grow, and remyelination take place. However, by the time the process of neural regeneration extends to the terminal end plates, the changes within the muscle, fibrous tissue, bone and joint structures may be so profound as to render them incapable of effective motion. It is the function of physical medicine to hold these atrophic alterations to a minimum. The necessity to do so is emphasized by the investigations of the changes produced by immobilization of the muscles of healthy young men. There occurred a deterioration in the mechanisms essential for adequate circulation, a decline in the basal metabolic rate, increased excretion of nitrogen, calcium, phosphorus, total sulfur, sodium and potassium, and a lowering of creatine tolerance.¹⁰ The disturbances in calcium metabolism can be responsible for the occurrence of renal calculi and of myositis ossificans.¹¹

Many of these considerations are exemplified in the treatment of peripheral paralysis of the facial nerve, commonly referred to as "Bell's palsy."

TREATMENT OF BELL'S PALSY

It appears to be the generally held idea that in as much as Bell's palsy is a disease from which the patient may recover spontaneously,

no effort should be made to treat him. This therapeutic nihilism might be justified on the basis that conclusive proof has not been presented thus far to indicate the possibility of exerting a specific influence on the diseased facial nerve. This attitude may not be completely defensible when one understands that there are two additional factors which merit therapeutic consideration. One is the alteration in the motor mechanisms responsible for the motions of the face which occurs secondarily to the interruption of the voluntary impulses. These secondary trophic changes in the facial muscles may prolong the period during which no motions are discerned, and may also be responsible for permanent disability. The other factor is the patient as a human being possessed of a psyche which can be tremendously disturbed when the victim realizes that his facial appearance has been altered profoundly and that in addition he now possesses some disturbing physical incapacities. The data which may indicate the reasonable possibilities of favorably influencing these two factors are both experimental and clinical.

Prevention of Stretching of Paralyzed Muscles. Ordinarily the muscles of both sides of the face contract simultaneously. It is questionable whether the muscles of the opposite side of the face relax completely when an effort is made at unilateral contraction. It is unfortunate for the sufferer from Bell's palsy that in every attempt at motion—as in talking, eating and registering emotion—the paralyzed muscles are pulled toward the uninvolved side. That such stretching is harmful is indicated by the experiments of Eisenhauer and Key,¹² who, working with the gastrocnemius-soleus group of muscles in cats, found that disuse atrophy is more marked in stretched muscles than in those maintained in the relaxed or neutral position. The clinical observations of Pickerill and Pickerill¹³ are in accord with these experimental findings. These surgeons noted, that if means to prevent stretching of the muscles was applied directly after the purposeful cutting of the facial nerve in the removal of parotid tumor, the muscles lost surprisingly little tone during the three-week interval before plastic surgery (consisting of fascia lata and muscle grafts) was performed, in contrast to muscles where no such care was taken to avoid stretching. These workers believe that the cause of life-long disfigurement for many people lies in the generally held notion that because a large percentage of Bell's palsies recover spontaneously, treatment is not given to them. They, therefore, urge that "in every case of Bell's palsy the only safe

procedure is to presume that it will not recover unless something more than an attitude of masterful expectancy is adopted." It is their belief that "probably the chief factor in non-recovery of what should be the temporarily paralysed muscles is their immediate and continued overstretching by the non-paralysed muscles of the opposite side of the face." The Pickerill technique is to hold the muscles on the good side by fastening adhesive plaster from the skin on this side to the region of the mastoid process on the paralyzed side. The plaster glides over the skin of the involved side because of vaseline or oil applied to it. The paralyzed orbicularis oris muscle is held in a sling made by stretching adhesive strips from the region of the eyebrow down and across each other below the eye. This, they maintain, serves to hold the lid in apposition to the eye, to prevent epiphora, and to counteract the weight of the paralyzed cheek and so prevent the orbicularis muscle from losing tone.

Pracy¹⁴ modified the Pickerill technique by having the adhesive which is stuck on the good side of the face extend to a wire loop which surrounds the mouth and is anchored by a "handle" going to and curving around the ear. This modification is designed to permit the more ready replacement of the adhesive when it becomes dirty or works loose and when it is removed to allow shaving.

The simpler and more commonly employed, though possibly not as effective procedure to counteract overstretching, is to hook a piece of covered wire around the corner of the mouth on the involved side. The other end of the wire is curved around the ear. This hook can be readily removed and replaced. A cosmetically better device designed for the same purpose is the removable intra-oral splint constructed by Allen and Northfield.¹⁵

Heat. It appears logical to apply a procedure to increase blood flow and to heighten the metabolism of muscles threatened with the atrophy which follows denervation. Local heating may well serve such purposes and also act as a preparation for whatever muscle contracting measures are deemed advisable. Experiments performed by Asmussen and Boje¹⁶ showed that a given amount of work could be performed better, i.e., in a shorter time, when the organism was warmed up by preliminary work. Also a greater muscular tension could be developed when "warmed up" than when not. Passive warming up by diathermy or by hot baths also increased the capacity for work. The conclusion reached

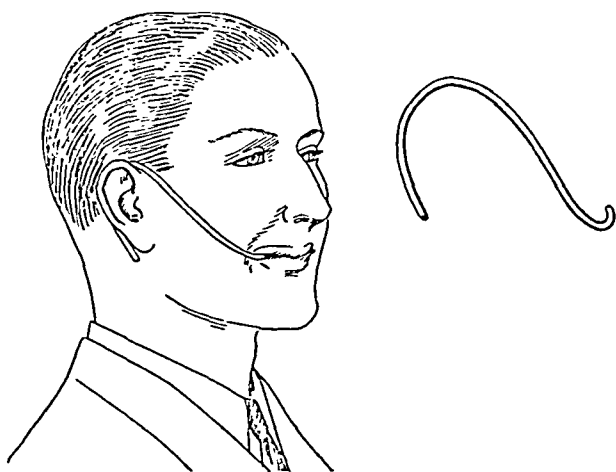


Figure 3—Wire splint for Bell's palsy.

from these results was "that a higher temperature in the muscles benefits the ability to perform work by accelerating the chemical processes in the muscles, probably also decreasing the intra-muscular viscous resistance."

All methods of heating are useful. A 1500 watt tungsten filament lamp has greater penetrating power than an infra-red lamp.¹⁷ If the patient is photophobic (in spite of goggles—which cover the eyes only) the infra-red lamp is applied. Inasmuch as the facial muscles lie but a short distance beneath the skin surface, it is not essential to use the conversion heating of diathermy.

Electrical Stimulation. There has been a difference of opinion concerning the therapeutic value of electrical stimulation and the advisability of its use during the first ten days of paralysis. Much experimental work has been done. The preponderance of experimental evidence favors the early use of such stimulation in the treatment of denervated muscles. Thus, Kosman and his co-workers,¹⁸ investigating the effect of electrical stimulation upon the course of atrophy and recovery of the gastrocnemius of the rat, found that the loss of weight and strength of experimentally denervated muscles can be effectively retarded by the use of electrical stimulation under the following conditions: 1) a current must be used which will produce maximal tension in the muscles within the limits of tolerance; 2) the muscle must be stimulated at frequent intervals; 3) treatment must be started soon

after denervation. Fischer and Ramsey¹⁹ observed that the daily electrical treatment of denervated rabbit muscles is effective in retarding weight loss and the deterioration of muscle protein. Following some earlier experiments, Fischer²⁰ concluded that the best results are obtained when the electrical stimulation is started immediately after denervation and that the strength and the duration of the electrical current must be adapted to the changing excitability of the atrophying muscles. He postulated that the electrical treatment causes mainly a training effect in the denervated muscle similar to that in the normal muscle, which only increases the size of the fibers and their metabolic capacity. Suskind et al²¹ reported that suitable electrical stimulation retards weight loss of denervated gastrocnemii in cats but exerts no effect on the contractile strength per unit of muscle. Kosman and his co-workers²² found that the best type of electrical current for muscle stimulation is a 25 cycle sinusoidal one. Another modification of the electrical current can be employed for its mild irritating influence. This is the static brush discharge.²³ During its use, we have occasionally observed contraction of muscles on the paralyzed side of the face when the patient has been unable to make any such voluntary motion. The reaction may be like that which occurs reflexly as when a fly alights on the face. While the reflex arc is supposed to be interrupted in damage to the facial nucleus or to the peripheral nerve (in contrast to a supranuclear lesion) it may be possible that not all the fibers are involved, as can be frequently demonstrated for the motor component of the nerve by electromyography, and that similarly reflex activity may exist though to a diminished degree.

If the palsy persists after two weeks, we apply electrical stimulation to the muscles of the face, usually at intervals of every other day. This timing is made as a matter of convenience. Such stimulation can be administered earlier (from the very beginning of the paralysis) and more frequently. We have observed no harm with such a regimen when we have followed it. Experimental evidence would indicate the advisability of this procedure.

Positive galvanism is applied to a painful region when present. The pain usually disappears in a few days. It has not been proven that the galvanism influences the pain, though this is our impression.

Massage. The layman often thinks of massage as a measure to be used in the treatment of paralysis—an opinion which he shares with

some doctors. Massage, if used, should be applied to paralyzed muscles with very mild pressure—as in effleurage. In the face, particularly, where a bony surface lies but a short distance behind the muscles, there is danger of mechanical traumatization. There is warrant for the use of massage as determined by the experiments of Suskind et al²¹ who found that massage causes only a slight retardation of the weight loss but proves to be effective in maintaining the strength of the denervated muscle. In massaging the face, the stroke should begin in the region of the chin and lip and proceed upward and outward to the area in front of the ear.

Exercise. Voluntary exercise is the most effective measure to improve muscle strength. However, the patient should not be requested to exercise a muscle until he has shown himself capable of producing voluntary motion in that muscle. In the care of Bell's palsy, extra caution is necessary because in the early stages of returning function the ability to cause unilateral movement on the involved side frequently is absent. In bilateral motion, the healthy side is the stronger and the weak muscle is in danger of being stretched. This danger may not be as great when the frontalis and orbicularis oculi show motor power and the patient is instructed to wrinkle his forehead or close his eye, as it is when he is requested to show his teeth. In the latter instance, it may prove helpful to have the patient manually restrain the activity of the muscles on the uninvolved side of the face while exercising the muscles on the paralyzed side. The patient should preferably exercise in front of a mirror and follow specific instructions.

General Therapeutic Considerations. The patient will frequently ask questions in addition to those concerning diagnosis and prognosis. These should be answered. He is told to avoid eye strain—as in reading and in looking at motion pictures. Some are helped by the wearing of colored glasses or an eye shield, particularly if there is marked ectropion. Washing with boric acid solution will help allay irritation of the eye. Chewing can be done on either side of the mouth, inasmuch as the masseter and buccinator muscles are not involved, but the patient may prefer to do most of it on his good side because food collects between the teeth and cheek on the paralyzed side. Some patients find that they can chew best when they use their hand to pull the involved cheek upward toward the ear. The answer to the question "Shall I go to work?" depends on the nature of the work. The preoccupation of activity is

TABLE III—DURATION OF PALSY: RESULTS ACHIEVED IN 100 CASES

<i>Number of Cases</i>	<i>%</i>	<i>Total %</i>	<i>Weeks</i>	<i>Number of Cases</i>	<i>%</i>	<i>Total %</i>
2	4		1			
20	36	41	2	9	20	
4	7		3	5	7	
13	24	71	4	5	11	38
2	4		6	3	7	
2	4		7	3	7	
<i>Months</i>						
5	9		2	7	15	
2	4	92	3	2	4	71
1	2		4	6	14	
2	4		5	1	2	
2	4	100	6	2	5	92
			7	1	2	
<i>Group "A"—Patients treated daily with</i>			8	1	2	
<i>Splinting, Radiant Heat and Static</i>			9	1	2	
<i>Brush Discharge.</i>			11	1	2	100
<i>Group "B"—Patients treated every other day with Splinting and Radiant Heat.</i>						

time period. At the end of a month 71 per cent of Group "A" and 38 per cent of Group "B" required no further treatment. After three months 92 per cent of Group "A" and 71 per cent of Group "B" were judged as needing no further care. The remaining 8 per cent of Group "A" continued to receive treatment during the following three months, at the end of which time the patients were discharged even though some residual weakness persisted. The termination of this additional three month period (a total of six months) still found 8 per cent of Group "B" requiring care which was continued for another five months. These findings clearly indicate that patients receiving daily treatment during the first two weeks with heat and static brush and subsequently interrupted galvanic stimulation do better than those whose initial therapy was heat and massage applied every other day and then interrupted galvanic excitation.

Not all patients make a complete recovery. In a few, some residual weakness may continue for a long time. A complication which occurs in cases of long standing is contracture. These patients may show a

narrowing of the palpebral fissure, deepening of the naso-labial furrow, and of the lines at the corner of the mouth. They may complain of a sensation of tightness in the muscles of the face and may experience intermittent muscle spasm. Feinstein²⁶ considers the contracture as due to a fibrous metaplasia inasmuch as there were numerous areas of electrical "silence" in the facial muscles when electromyographic examinations were made.

Another annoying sequel is the inability to contract individual muscles after the return of motor power. The muscles may move in groups. The associated movements were accounted for on an anatomical basis by Howe, Tower and Duel²⁷ who found that many of the regenerating axons do not follow their original pathways and dichotomization of the axons is frequent. More recently Weiss and Edds,²⁸ on the basis of studies on incompletely denervated muscles in laboratory animals, concluded that spontaneous recovery is due to the fact that intramuscular branches of the intact motor fiber undergo additional branching and take over the supply of denervated muscle fiber. This occurs only when intact and denervated elements lie intermingled. The ultimate prognosis for the independent movements of the facial muscles is poor in view of this abnormal pattern of innervation.

Several surgical methods of treatment have been recommended for persistent palsy. These include anastomosis of the facial nerve with some other nerve in the neck; direct line repair utilizing a branch of the anterior crural, and the uncovering of the nerve in the Fallopian aqueduct followed by its decompression by incision of the sheath.^{29,30} Plastic repair has also been advised with fascia lata and muscle grafts and with tantalum wire or ribbon.³¹ A critical comparison of the results obtained by surgical means and by prolonged conservative treatment remains to be made.

SUMMARY AND CONCLUSION

Experimental and clinical evidence has been presented to indicate the importance of the early application of the measures employed in physical medicine in the treatment of Bell's and other palsies.

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RECENT ADVANCES IN THE DOMAIN OF THE ANTI-HISTAMINE SUBSTANCES: THE PHENOTHIAZINE DERIVATIVES*

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WE HAVE studied recently a new series of anti-histaminics. Chemically they are derivatives of phenothiazine. The most active of the series is N-dimethylamino- 2-propyl-I-phenothiazine. The anti-histamine properties of this synthetic substance were discovered in France in 1946¹ and have been intensively studied there since.

HISTORICAL SURVEY

The first synthetic substance reported to possess anti-histamine properties was described by Fourneau and Bovet in 1933² and later by Staub and Bovet.³ This was 929 F or thymoxyethyl-dimethylamine. In 1937 Bovet and Staub⁴ also described 1571 F a derivative of ethylene diamine. Both these substances showed only moderate activity and were too toxic for therapeutic administration.

In 1942 Halpern⁵ showed that N-dimethylaminoethyl-N-benzyl-aniline (Antergan or 2339 RP) was more powerful and less toxic than the earlier products and the first clinical trials were attempted.

During the years which followed, various modifications of Halpern's drug were produced, such as Neo-antergan (Bovet and Walthert, 1944⁶), Benadryl (Loew, Kaiser and Moore, 1945⁷) and Pyribenzamine (Mayer, Hutterer and Scholtz, 1945⁸). Numerous comparative studies have been made, notably by Code⁹ and by Feinberg,¹⁰ as well as the many studies on the experimental activity of each substance separately.^{11, 12, 13}

In 1946, Halpern and Ducrot¹ showed that certain phenothiazine derivatives possessed anti-histamine properties which were in many respects more powerful than those of any previously described sub-

* From the Clinique Medicale Propedeutique, Hopital Broussais, Paris (Professeur Pasteur Vallery-Radot).
Given October 11, 1948 before the 21st Graduate Fortnight of The New York Academy of Medicine.

stance. A series of experiments was made to study the activity of this new group of substances, particularly N-dimethylamino-2-propyl-1-phenothiazine, known as 3277 R.P. or Phenergan.¹⁴

EXPERIMENTAL FINDINGS

Phenergan possesses the same well-established properties as the other anti-histamines, but quantitatively its action is much more powerful in many respects.

1) The antagonism of Phenergan to histamine is well shown in experiments on the smooth muscle of the bronchi, intestine and uterus and by its inhibition of the Triple Response of Lewis and of the histamine effect on the blood pressure.^{5, 7, 15, 16}

The degree of protection against histamine conferred by Phenergan, is much greater than that given by any other anti-histamine substance. A dose of Phenergan of 20 mgm. per kilo protects the guinea pig against 1,500 and the rabbit against 450 lethal doses of histamine.

2) The anti-anaphylactic effect is equally striking. Phenergan counteracts anaphylactic shock and prevents the Prausnitz-Kustner reaction. This action is much greater than that of the other anti-histamine substances.

3) The duration of action of Phenergan is much prolonged. For example, the duration of action against experimental asthma in the guinea pig is 3 times as long as the action of Antergan or Neo-Antergan under the same conditions.

Studies made in man¹⁷ by following the intradermal histamine response after oral administration of various anti-histamines have shown that the duration of action of Phenergan is quite remarkable in the slowness with which it disappears.

4) Phenergan, like the other anti-histamine substances, cannot, however, counteract the effect of histamine on the secretions. Hence, animals given large doses of histamine after the administration of Phenergan show no immediate signs produced. This probably explains the constant appearance of gastric ulceration under such conditions.¹⁸

5) Last and Loew (1947)¹⁹ had already demonstrated by Menkin's method that Benadryl and Neo-Antergan counteract the local increase of capillary permeability induced by histamine. By noting the penetration of fluorescein into the anterior chamber of the eye^{20, 21} and by the diffusion of dyes into peritoneal exudates it has been shown that Phen-

ergan powerfully opposes the increase of capillary permeability produced by histamine and various other substances.

6) Two special effects of Phenergan, possibly due to its more powerful action on capillary permeability have been investigated.

a) Phenergan prevents the appearance of the acute pulmonary edema, which is induced in unprotected animals by intravenous epinephrine¹⁶ or by certain poison gases, such as chloropicrin or phosgene.²²

b) Phenergan prevents the induction of experimental orthostatic albuminuria in rabbits.²³

7) Phenergan has shown in various functions a non-negligible atropine-like activity.

CLINICAL STUDIES

Methods: Phenergan was administered orally in the form of 25 mgm. tablets. The usual dose varied between 25 and 100 mgm. daily, but in certain cases, up to 200 mgm. were given. Blood counts were carried out before and every two weeks during treatment. Allergic clinical and skin tests were carried out before and during treatment whenever possible.

Results: a)—*Serum sickness.* Seventeen cases of serum sickness were treated. In each case the skin manifestations, such as pruritus and urticaria, disappeared within from 30 minutes to 3 hours after administration of the drug. Joint pains were present in four patients and disappeared under treatment in only two of the cases. The fever was scarcely influenced.

b)—*Urticaria.* One hundred and twenty-three cases of urticaria of varying origin have been treated. In only twelve of these cases could an allergic basis be demonstrated by clinical and cutaneous tests.

One hundred and eight cases (87.8 per cent) showed immediate improvement. The pruritus was the first symptom to disappear; then the skin reaction tended to diminish and had often entirely disappeared after a few hours. Of the remaining fifteen patients, six showed signs of intolerance and were unable to continue treatment, while nine cases were little, or not at all, benefited by the drug. All the cases of definitely allergic origin improved under treatment, but among the successes were several cases in which there was no reason to suspect any such cause. About 60 per cent of the successful cases had previously failed to respond to Neo-Antergan.

c)—*Angioneurotic edema*. Out of nineteen cases of angioneurotic edema, only three were not improved by treatment (84 per cent of favorable results). Two of the successful cases were patients in whom edema of the lips had persisted in between the acute exacerbations.

Apart from these cases of true angioneurotic edema, there were two patients who suffered a local edema after the slightest pressure on any part of the body. These cases were uninfluenced by Phenergan.

d)—*Pruritus*. Out of 18 cases of prurigo from varying causes, six were not influenced by Phenergan, but 12 were vastly improved, the pruritus ceasing even when the visible lesions persisted unchanged. Included in these 12 are several cases of pruritus due to scabies.

e) *Eczema*. None of our seventeen cases of chronic eczema was completely cured by treatment. In a few cases slight relief was obtained, especially from the subjective symptoms such as pruritus.

Out of twenty-two cases of acute eczema and contact dermatitis, three showed rapid improvement which ended in complete cure. The rest of the cases improved only after a much longer period and it is difficult to assess the influence of Phenergan on these results.

Three cases of arsenical and one case of gold erythrodermia showed no real improvement on treatment with Phenergan.

f)—*Allergic purpura*. One case of allergic purpura, in which new crops of petechiae appeared daily for three weeks before treatment, was treated with Phenergan. Administration of the drug was followed by immediate cessation of fresh eruptions.

g)—*Hay fever*. One hundred and forty-two cases of hay fever were treated between the spring of 1947 and that of 1948; ninety-eight cases (69 per cent) showed complete disappearance of all signs and symptoms; thirty-six cases were only partially relieved; the sneezing ceased but the nasal congestion remained more or less the same; eight cases were completely unchanged by treatment but most of these were unable to tolerate full doses of the drug.

It should be noted that, in the majority of cases, 25 mgm. of the drug daily suppressed sneezing, but a dose 4 to 6 times as great is usually necessary to give complete relief from all the symptoms. For a few patients, however, 6-12 mgm. daily sufficed to suppress all symptoms.

At a recent meeting of the French Society of Allergy (June 15th, 1948) Pasteur Vallery-Radot, Blamoutier and B. N. Halpern have com-

municated statistics of 200 cases of hay fever treated with Phenergan with a dose of 25 mgm. to 50 mgm. daily; they reported 86 per cent of excellent results with relief of all symptoms; in only 14 per cent the improvement was incomplete.

h)—*Asthma*. Seventy-two cases of asthma were treated but an allergic basis could only be demonstrated in 9 of them. In all these 9 cases, considerable relief or even complete disappearance of the asthma was obtained. In 21 other cases without any appreciable allergic origin, there was a certain degree of improvement. In the remaining 42 cases, the results were completely negative.

i)—*Spasmodic cough*. Nine cases of spasmodic cough were entirely uninfluenced by treatment.

j)—*Migraine*. Out of twenty cases of migraine, six were improved by Phenergan.

It was impossible to determine an allergic basis for any of these 6 cases.

k)—Phenergan appeared to have no effect on chronic or subacute rheumatism or on acute glomerulo-nephritis. It did not seem to influence the allergic manifestations of tuberculosis, or the intradermal tuberculin test. This latter observation is in contrast to its action on allergic skin tests for other diseases. In such cases, whenever skin tests were found to be positive before treatment, immediately after adequate dosage with Phenergan they became temporarily negative.

Tolerance and side-effects. The drug was usually well tolerated. In particular, it did not provoke the digestive upsets which often occur with the other anti-histamine substances.

The blood picture was affected in only two cases, a slight neutropenia being observed. Administration of the drug was immediately stopped.

The only important side-effects were of nervous origin. About 25 per cent of the patients showed a certain degree of drowsiness accompanied by vertigo and instability when standing upright and by sensations of drunkenness. Occasionally there was also a slight decrease in intellectual power. In rare cases, insomnia occurred rather than drowsiness.

These troubles, which are impossible to predict and which may occur even with feeble doses, constitute the most serious disadvantage to the use of Phenergan. Usually they seem to be partially neutralized

Condition	Total No. Treated	Cure		Improvement		Failure	
		Actual No.	%	Actual No.	%	Actual No.	%
a. Serum sickness	7			7	100	0	0
b. Urticaria							
1/Def. allergic	12		← 12 →		100	0	
2/Aet. unknown	111		← 96 →		86.5	15	13.5
Total	123		108		87.8	15	12.2
c. Angioneurotic edema	19	0	← 16 →		84	3	16
Pressure edema	2			0		2	
d. Pruritus	18		← 12 →		67	6	33
e. Eczema							
1/Acute & contact	22			3	13.6	19	86.4
Chronic	17			0	0	17	100
Total	39			3	7.7	36	92.3
2/Erythrodermia gold and arsenic	3	0		0	—	3	100
F. Allergic purpura	1	1					
g. Hay fever	142	98	69	36	25.3	8	5.7
h. Asthma							
1/Def. allergic	9		← 9 →		100	0	
2/Aet. unknown	63	0		21	33.3	42	66.6
Total	72			30	41.7	42	58.3
i. Spasmodic cough	9	0		0		9	100
j. Migraine	20			6	30	14	70
K. Other conditions—Acute and subacute rheumatism, tuberculous allergy, acute glomerulo-nephritis—uninfluenced.							

K. Other conditions—Acute and subacute rheumatism, tuberculous allergy, acute glomerulo-nephritis—uninfluenced.

by the simultaneous administration of Benzedrine. Moreover, the nervous troubles almost always disappear within a few days, even if treatment is continued with the same dose.

The drowsiness may be neutralized if Phenergan is given at night. This effect wears off before morning but the true action of the drug continues throughout the following day.

DISCUSSION

The experimental and clinical results described above lead us to consider Phenergan as a powerful anti-allergic substance. However, several conditions in which no allergic cause could be demonstrated, were influenced by the drug. These were:

- a) Experimental syndromes such as acute pulmonary edema due to epinephrine or poison-gas; orthostatic albuminuria;
- b) Clinical cases of migraine, certain skin conditions and some asthmas. On the other hand, a certain number of definitely allergic conditions were not benefited by the drug; for example, all chronic and most acute cases of eczema.

In consequence, the problem of the mechanism of action of Phenergan still has to be elucidated. The first theory was that histamine is responsible for non-allergic syndromes influenced by Phenergan. Up to the present there has been no serious proof of this. The experimental work described above suggests that Phenergan acts on capillary permeability. In this connection, it is very striking that most of the pathological conditions controlled by Phenergan are characterized by serious extravasation through the capillary wall, for example, experimental acute pulmonary edema and orthostatic albuminuria, urticaria and even, perhaps, migraine.

SUMMARY

1) Experimental work on Phenergan, a phenothiazine derivative which is a powerful new anti-histamine substance, is described. Apart from its action on allergic conditions, it prevents the production of experimental acute pulmonary edema and orthostatic albuminuria.

2) Clinical trials with this substance proved it to be of value against serum sickness, urticaria, angioneurotic edema, hay fever and allergic purpura.

Less success attended the use of Phenergan in cases of asthma, migraine and pruritus, with almost none against the eczemas.

3) The mechanism of action of Phenergan is discussed. The experimental and clinical evidence is in favor of its action on capillary permeability.

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BULLETIN OF THE NEW YORK
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CONTENTS

Topectomy—Surgical Indications and Results	335
<i>J. Lawrence Pool, Robert G. Heath and John J. Weber</i>	
Therapy of Asthma with Reference to Its Psycho- dynamic Pharmacology	345
<i>Harold A. Abramson</i>	
Medicine Under Mussolini	364
<i>Mario Volterra</i>	
Section on Microbiology	
Chemical Aspects of Some of the Newer Insecti- cides, <i>H. L. Haller</i>	374
The Major Toxic Actions of Insecticides, <i>Arnold J. Lehman</i>	382
Recent Advances in Medical and Veterinary Ento- mology, <i>E. F. Knipling</i>	388
Library Notes:	
Recent Accessions to the Library	397
Communication to the Editor	400
Announcement	400

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MAHLON ASHFORD, *Editor*

Published Monthly by THE NEW YORK ACADEMY OF MEDICINE
2 East 103 Street, New York 29, N. Y.

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BULLETIN OF
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JUNE 1949

TOPECTOMY:
SURGICAL INDICATIONS AND RESULTS*

J. LAWRENCE POOL, ROBERT G. HEATH, and
JOHN J. WEBER

TOPECTOMY (from "topos," place; "ektome," a cutting-out)¹ is an operation consisting of limited bilateral ablation of cortex from the frontal lobes for the treatment of mental illness. While cortical ablation² or frontal gyrectomy³ are also acceptable terms, topectomy is more concise and perhaps more accurate because it signifies a topical resection of cortex according to the approximate limits of Brodmann's areas or portions thereof, whereas frontal gyrectomy suggests removal according to specific frontal gyri.

Topectomy has evolved after considerable trial into a fairly standard type of operation involving bilateral removal of the rostromedial portion of each frontal lobe, believed to represent (approximately) the medial portions of areas 9 and 10 of Brodmann.⁴ Cortical removals are begun 2.5 cm. in front of the coronal suture when it crosses the midline, and thence extend 5.5 cm. anteriorly; 3.5 cm. laterally; and 1.9 to 2.0 cm. in depth. Each excision is thus carried to the depths of the gray matter but not into the underlying white matter as in lobotomy. Hence topectomy spares a great deal more of both the gray and the

* Presented March 3, 1949 before the Stated Meeting of The New York Academy of Medicine. From the Service of Neurological Surgery, Neurological Institute, New York.

white matter of each frontal lobe than does lobotomy, and is accordingly in this respect a more conservative type of operation.

General Indications: Any attempt at surgical relief of mental illness is, in general, indicated only when other appropriate types of therapy have been tried and have failed. In all but two of our cases, insulin or electrical shock treatment as well as psychotherapy had been used without lasting success before operation was carried out.

Specific Indications: Specific indications for topectomy are essentially the same as for prefrontal lobotomy, with one notable exception: Topectomy, being less radical as to the amount of brain tissue sacrificed, is in general not indicated for the purpose of rendering a violently assaultive psychotic patient into a tractable but perhaps apathetic automaton. (A more detailed description of the indications for topectomy is now in preparation.)

Type of Patient: As a result of analyzing post-topectomy effects in the chronic, deteriorated "back" ward schizophrenic as well as those in the more acute, less deteriorated group, it appears that the best results may be expected in those schizophrenic patients who still manifest at least some evidence of "drive" and some indication of emotional reaction or affect. Although there are exceptions our results indicate in general that the patient's age at the onset of illness, previous response to shock treatment, duration of illness, and perhaps the intellectual level are important prognostic considerations. Thus schizophrenic patients over 45 years of age usually fail to profit by operation, especially if symptoms have been prominent for many years and appeared early in life. Another extremely important factor in selecting candidates for topectomy, as it is for lobotomy, is the social background. We have found that a sympathetic and helpful climate in the patient's home is virtually imperative if a good result is to be maintained. It is, of course, also most important that follow-up psychotherapy be available if the initial gain following operation is to be extended. The majority of patients referred for topectomy have been schizophrenic but this group is not the only one in which improvement occurs. Other categories of mental disturbances for which topectomy is indicated are obsessive-compulsive neurosis and depressions that do not respond to the usual types of treatment. Results have been best in the obsessive-compulsive group and the affective disorders including involutional depression, agitated depression and the depressed phase of the manic-depressive

psychosis. Poor results were obtained in reactive depressions associated with Parkinson's disease; and two psychopaths responded poorly although there are theoretical reasons to expect a favorable response in some members of this group. Good results without personality changes have been reported following a less radical bilateral topectomy for the relief of intractable pain, but the authors have had no experience with this use of topectomy.

INCIDENTAL OBSERVATIONS

Pathology: Certain interesting and perhaps valuable observations have been made during the course of topectomy operations owing to the rather generous exposure of the brain they require. First and foremost is the fact that my associates and I, and other neurosurgeons with experience in this field, have noted that a large percentage of psychotic patients appear to have a grossly abnormal brain both as to appearance and consistency. Approximately two-thirds of our patients clearly seemed to have gross abnormalities of the brain at operation:— 23 of the 36 schizophrenics, and 14 of the 18 patients in the other groups. These changes were characterized by definite reduction in the size of the cerebral gyri, a marked increase of the subarachnoid fluid, and a thickened, hard or rubbery consistency of the underlying brain. In some cases the cortex was yellowish; in others, there seemed to be an excess of small cortical blood vessels, while in many the arachnoid membrane was not transparent as in the normal state, but milky, translucent or spotted. Finally, in many cases the cingulate gyri were found to be densely adherent by arachnoidal adhesions, as if glued together. In contrast, the brains of the remaining third of our patients thus inspected seemed entirely or almost normal, particularly those of the obsessive-compulsive group. It thus seems clear that many psychotic patients harbor a grossly pathological looking brain. The significance of this observation is not apparent, especially as microscopic analysis fails to reveal very much beyond scattered shrunken or distorted and deeply staining nerve cells. Specific changes in the oligodendroglial cells were not demonstrable.⁵ Perhaps the observed gross changes at operation indicate disturbed cerebral metabolism, as yet unexplained, along the lines suggested by Stockings.⁶ Certainly the pathological changes cannot be ascribed to shock therapy as they were present in several patients who had not had shock treatment, and conversely were not found in

some patients who had undergone extensive shock treatment. Nor is age necessarily a factor as two schizophrenic patients were quite young and yet showed advanced pathological changes, while several patients in the fifth or sixth decades presented quite normal looking brains.

As to a correlation between cortical atrophy and postoperative results:—Of those patients with a moderate degree of cerebral atrophy, approximately half showed postoperative improvement while the other half failed to improve after topectomy. While a few with advanced atrophy improved a great deal and a few with a normal looking brain failed to improve, in general those with advanced atrophy failed to improve, while those with normal looking brains seemed as a group most apt to improve.

AUTONOMIC NERVOUS SYSTEM

Effects upon the autonomic nervous system often become manifest following topectomy as they may after lobotomy. Many patients tend to gain weight, perhaps in part because their anxiety has been lessened, while a few that do not improve may lose weight. Two hypertensive patients have maintained a marked reduction in their blood pressure after topectomy, one for two years. Others may show temporary improvement in the peripheral circulation; while after some of the early area 9 (Brodmann) ablations, retention of urine occurred for some days that may represent a "release" effect upon the bladder complex of the cerebral cortex. Finally, it may be appropriate to mention the effects of stimulation of the cingulate gyri in its rostral portion, which in the experimental animal has been shown to elicit profound alterations in the heart rate, blood pressure and respiratory rate. It can now be said that the same phenomena follow electrical excitation and even mechanical stimulation of the rostral cingulate cortex in man.⁷ This is an observation that may sometime prove of value in the treatment of diseases referable to the autonomic system.

AMOUNT OF CORTEX

Before turning to the actual results of topectomy the amount of cortex sacrificed by the operation should be considered, for careful analysis of this factor suggests two things: first, that an adequate amount of cortex must be removed if a good result is to be obtained; and secondly, that in some cases (particularly the advanced chronic or

deteriorated schizophrenic), no matter how much cortex is removed there will be no significant improvement, at least as far as social rehabilitation is concerned. These two views suggest as a corollary that if an adequate amount of cerebral tissue is removed (and the amount can be quite well judged by measurements and weights of the ablated tissue) there is as a rule no value in removing further cortex if the psychotic condition fails to improve.

Removal of about 30 grams for *each* frontal lobe seems to be the average effective amount. Somewhat more than this has had to be removed in a few chronic schizophrenics at a second operation before improvement took place, while less than this amount has proved effective in depressed or obsessive states.

In a word, topectomy has proved an excellent opportunity for arriving at some idea of whether or not a quantitative factor is important in frontal lobe operations of this kind. It is our feeling that a quantitative factor is important. However, we also feel that the qualitative or anatomical factor is important, on the basis of this and other work of a similar nature and certain laboratory data. Perhaps one reason that ablation of cortex from the region of what we believe represents the rostro-medial portions of areas 9 and 10 of Brodmann, is that this region is an important station for thalamocortical projections (especially those of the dorso-median nuclei of the thalamus).^{8, 9, 10} Interruption of this circuit seems to be a vital factor in reducing the anxiety underlying psychoses and other mental states, and of course this reduction of anxiety is one of the chief aims of psychosurgery.

Results of Topectomy—1. *Postoperative course*: The postoperative course is generally marked by immediate signs of improvement if the eventual outcome is to be successful. About 24 hours after operation, however, there may be an accentuation of psychotic manifestations or abnormal behavior, particularly in expressions of hostility and resentment. Hallucinations may or may not disappear at this time. Four or five days later improvement begins to be apparent, and from then on there is usually a steadily improving course in the favorable cases. For a period sometimes lasting weeks or months, there may be some degree of euphoria or dulling of mental acuity and "drive," although this is not invariably so. Such a picture usually appears in the schizophrenics and appears to be more related to the pre-existing psychopathology than to the operation. Fatigability is often slow to disappear, while

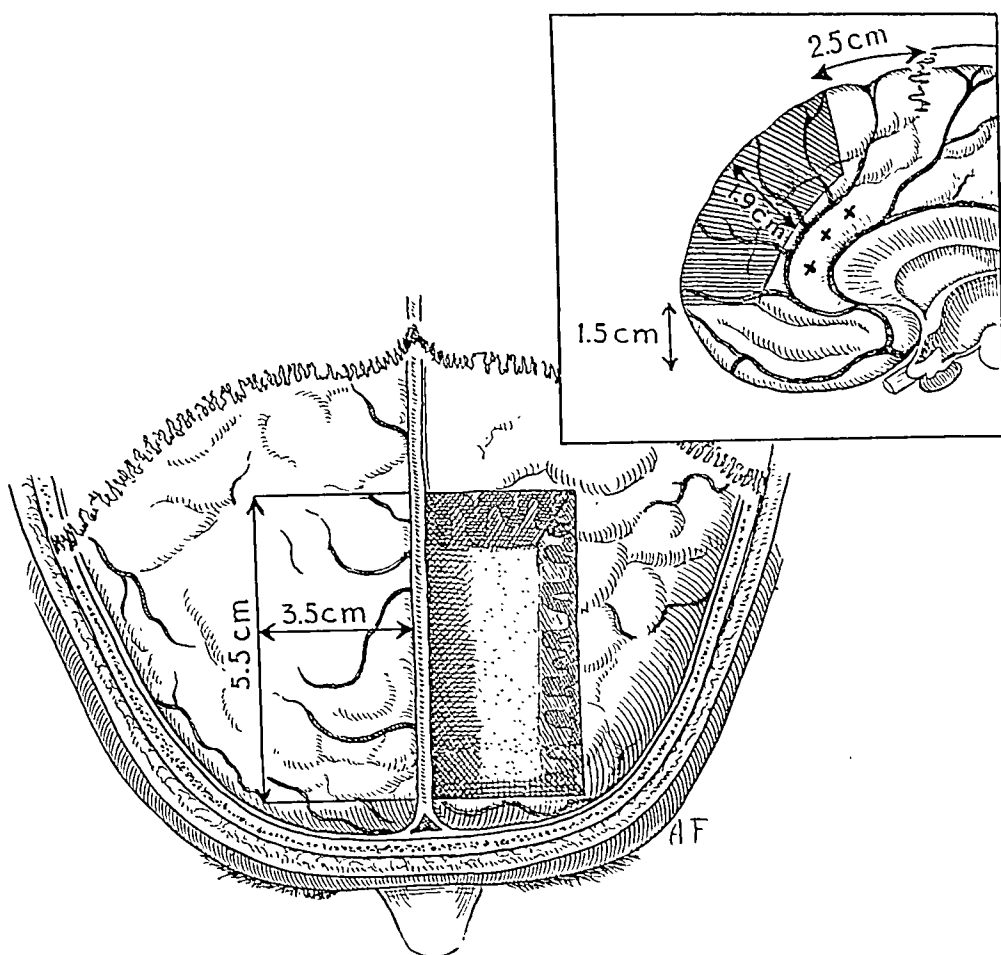


FIGURE 1.—Diagram showing approximate site and extent of cortical excision in topectomy. Excision is greatly simplified if the branches of the anterior cerebral arteries on the medial surface of the frontal lobes (shaded area in inset) are ligated with silver clips before attempting ablation. Large venous channels can then be secured between silver clips while smaller vessels may be lightly cauterized with the electrocautery. (Silk ligatures are no longer used). The cortex is then cleanly incised with a No. 11 scalpel all around the margins of the shaded area and removed as one block. Care is taken that the blade goes no deeper than 1.9 cm. (the average depth of the gray matter). Before closure, the margins of the cavity are made even with a small calibre suction tip and meticulous hemostasis is secured. The dura is closed in water-tight fashion, the bone flap anchored in place, and the anterior burr holes covered with small tantalum discs. A drain is seldom necessary.

NOTE: Crosses (X) on rostral aspect of cingulate gyrus indicate regions yielding autonomic responses on electrical or mechanical excitation.⁷

technical ability is seldom affected after topectomy, so that musicians and painters, for example, usually resume their special work within two weeks after topectomy.

2. *Incontinence*: About one-third of our patients are temporarily incontinent of urine for 2 to 23 days and a few have been doubly incontinent, but only temporarily. None have been permanently incontinent so far as we know.

3. *Mortality*: There have been no deaths in this series of 54 consecutive topectomies performed during the last 2½ years, all of whom have been followed for at least six months. A total of 92 topectomy operations has now been done by one of the authors (J.L.P.) including 6 re-operations, with no operative fatalities, and in an additional 25 cases done by other neuro-surgeons, only one fatality has been reported. The overall mortality rate is thus less than 1 per cent, which compares favorably with the postlobotomy mortality rate with ranges from 1.5 per cent¹¹ to 6 per cent.¹²

4. *Convulsive seizures and electro-encephalogram (EEG)*: Five of these 54 patients have had one or more postoperative convulsive seizures; that is, 10 per cent (Lobotomy: 7-11 per cent). All, however, are controlled by proper medication. In 4 the brain looked grossly abnormal at operation, but in one it did not. All of those who developed seizures and who had an EEG, showed abnormal activity in the frontal region bilaterally. One other patient had spiking in the prefrontal leads but did not have seizures, possibly because of precautionary anti-convulsant medication. Almost all other patients who had an EEG showed some abnormality in the prefrontal and often the temporal leads for 3-4 weeks, and occasionally longer, after operation. However, in most cases tested 6 months or more after topectomy, the EEG was reported as within normal limits. This observation is in keeping with the fact that so far none of our patients has developed seizures if they had been free of this complication for six months after operation. It may be added that in all our cases except one the pre-operative EEG was normal; and that anti-convulsant medication was never given unless indicated.

In the above 6 cases, seizures occurred regardless of whether the cortical ablation had been done with silk ligatures (2 cases), without ligatures (2 cases) or by the sub-pial technique (1 case).

5. *Other postoperative complications*: Two cases in this series were

TABLE I

Results are tabulated according to diagnosis and degree of improvement in 54 patients operated upon (topectomy) from October 1946 to September 1948. Marked improvement is rated as 4; moderate as 3; no improvement as zero; etc. This system of scoring, which takes into account the postoperative psychiatric status together with the degree of social rehabilitation, will be described in detail together with full case histories, in a subsequent communication now in preparation.

Diagnosis	Degree of Improvement—3-1-49					TOTAL
	4	3	2	1	0	
Schizophrenia (all types).....	7	8	5	2	14	36
Manic-Depressive—Depressed	2					2
Manic-Depressive—Manic					1	1
Involitional Depression	2		1	2		5
Agitated Depression		1	2			3
Reactive Depression — Parkinsonism.....					2	2
Obsessive-Compulsive—Neurosis	3					3
Psychopath			1			1
Schizoid Psychopath				1		1
TOTAL.....	14	9	9	5	17	54

re-operated upon within three days after operation because of an extradural hematoma. Both had a very vascular dura and both made a rapid and completely non-eventful recovery. Another patient developed signs of peripheral neuritis, apparently due to avitaminosis secondary to deficiency in diet prior to operation. This rapidly improved with a high vitamin diet.

6. *Tabulation of results:* This series of 54 patients represents all cases on whom a topectomy was performed with cortical ablation from what was believed grossly to represent the approximate region of Brodmann's areas 9 and 10. In the bulk of these cases sub-total ablation of areas 9 and 10 together was done. The group includes an almost equal share of patients presumed to have had a reasonably good prognosis and those who were obviously deteriorated. Various categories were included with the idea of helping some patients who could not find help otherwise. It is to be hoped in the future, however, that as a result of this evaluation cases will be more carefully selected. (The bulk of the schizophrenic group, it should be stated, were of the paranoid type. Of three catatonic patients in the schizophrenic group, two made a significant improve-

ment). When improvement occurred in any of these groups it was usually apparent within three months. There was, however, one exception where improvement took place six months after operation. Only two relapses have so far occurred in any of the patients who had showed a reasonable degree of initial improvement, and these occurred 8 and 16 months after operation. With two possible exceptions we do not think any of our patients have been rendered the worse for their operations.

As for the results, they compare favorably with most of the published data on lobotomy, as is shown in Table I based on a strict and conservative evaluation of our cases. Thus we have obtained approximately 20 per cent good results in our schizophrenic cases while Poppen also reports 20 per cent *good* results in this type of patient following prefrontal lobotomy.¹³ Another 20 per cent of our cases are significantly improved, so that they are at home and capable of housework, etc. but are not capable of earning their living. Those who are improved but still remain in an institution or even at home but who require care, are listed with our poor results; that is, with those cases who showed no improvement.

Of our best cases, their families say that they are the same as they were before their illness began. Those who worked are back at work, one as an accountant, another as a business man and others as secretaries, writers and housewives.

SUMMARY

1. The operation known as topectomy is described as bilateral ablation of cortex from the rostro-medial portion of each frontal lobe, believed to be portions of Brodmann's areas 9 and 10.

2. The selection of patients is discussed, and it is urged that in the future the selection of cases for psychosurgery be more carefully carried out. The obsessive-compulsive and certain forms of depression profit most by topectomy. The deteriorated and deeply regressed schizophrenic and the psychopath apparently profit the least. Some manic-depressives in the depressed state may do very well.

3. The postoperative results in mentally disturbed patients are tabulated. Our results compare favorably with lobotomy results, and in this regard it may be said that we have had few of the profound and permanent personality disturbances that may follow prefrontal lobotomy.

4. Postoperative complications include temporary but not perma-

nent incontinence in about $\frac{1}{3}$ of our cases; a 10 per cent incidence of seizures, all controlled by appropriate medication; two cases with post-operative hematoma, both successfully treated; and one case with peripheral neuritis, improved by appropriate treatment. The operative mortality rate has been zero.

5. It is currently our feeling that benefits from brain surgery in the mentally and emotionally sick may be attributed to two factors: one—quantitative, and the other qualitative or anatomical.

6. The electro-encephalogram has usually shown changes for a few weeks after topectomy, as it may after lobotomy, but in most instances shows no abnormalities six months after topectomy except in cases developing seizures.

7. Autonomic effects referable to the frontal lobes in man are briefly discussed, particularly as to stimulation of the rostral cingulate cortex.

8. Attention is directed to the impression that approximately two-thirds of our patients seemed clearly to have grossly pathological brains, although microscopic analysis failed to corroborate this impression. This suggests the urgent need for other types of study and analysis of the brains of psychotic patients, as a clue to the possibility of organic factors associated with certain mental diseases.

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THERAPY OF ASTHMA WITH REFERENCE TO ITS PSYCHODYNAMIC PHARMACOLOGY*

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It is my privilege to discuss certain aspects of bronchial asthma essentially produced by immunologic or allergic mechanisms. Although the origin of asthma is intimately connected with antigen-antibody reactions or allergen-antibody reactions, it will also be necessary to briefly explore the role of psychodynamics in implementing more effective therapy.^{1,2}

Let us first consider the nature of the immunologic process by analyzing the molecules responsible for pollen asthma. There is no doubt that in hypersensitive individuals, contact of sufficient pollen with the respiratory tract results in bronchial spasm as well as vasodilatation and swelling of the allergic mucous membrane. What is the nature of the molecules in the ragweed pollen granules or in timothy pollen granules which dissolve in the liquid film of the mucosa of the respiratory tract to diffuse into the tissues to cause pollen asthma?³ One of the most characteristic properties of any molecule is its size in terms of molecular weight. Do the allergenic molecules in ragweed and in timothy grass pollens have the high molecular weights characteristic of proteins? It had been proposed that these allergenic molecules are protein in nature. If they were proteins, we would expect comparatively high molecular weights. Recall for a moment the molecular weights of some common substances. The molecular weight of sodium chloride is approximately 58; that of histamine about 111; of sucrose close to 342.

If we examine the molecular weights of proteins, it is evident that

* Friday Afternoon lecture at The New York Academy of Medicine, December 10, 1948. From the First Medical Service and the Laboratories of the Mt. Sinai Hospital, New York City. These investigations since 1938 were supported by the Josiah Macy, Jr. Foundation, New York City; The Asthma Research Foundation, Boston; The Foundation for Research in Pulmonary Diseases, in New York.

the smallest molecular weight found for a typical protein, namely lactalbumin, is 17,000. Where do the allergenic molecules of ragweed and timothy pollens fit into this picture? In the last decade there have been devised precise methods of determining the molecular weights and other properties of protein molecules. These methods have made obsolete a good many of the early notions of the properties of protein molecules and have led to a more scientific description and elaboration of the nature of protein and allergen molecules. These methods are electrophoresis, ultracentrifugation and diffusion. For our present purposes, only electrophoretic and the ultracentrifugal data will be discussed.

The moving boundary method of Tiselius was used to separate the molecules of giant and dwarf ragweed extract.⁴

The dynamic process occurring in the U-tube is dependent upon the fact that the electrical charges of the components of the solution are different. In this way separation is achieved by means of electrical forces. e.g., electrical fractionation. Using this electrical method, it was found that in giant ragweed, dwarf ragweed, and timothy grass as well as in other pollen extracts, the main component was colorless in the concentrations isolated and practically without any motion in the electrical field. It was biologically active.

That is, this main colorless component was in each case a powerful allergen which produced hay fever and asthma as well as positive skin reactions. There was thus isolated, what are known as electrophoretically homogeneous allergens which were the main components as determined by electrophoretic fractionation. Separated from the complicated solution of pollen extracts were many pigments, which were also biologically active as far as could be ascertained with the small quantities available.

What sort of molecules were these major colorless components in pollen extracts?⁵ Were they very large molecules, as large as protein molecules or were they small molecules? Did they have chemical reactions characteristic of proteins? To ascertain the size of the essentially colorless molecules the electrophoretically homogeneous solutions were studied in an ultracentrifuge. The ultracentrifuge is really a more powerful centrifuge which is able to spin down protein molecules the way fat globules are spun down in a cream separator. The speed with which the molecules are sedimented gives an idea of the radius of the

molecule. By means of diffusion data and other characteristics of the solution, a very close approximation of the molecular weight is obtained. Study of the sedimentation velocity of the unpigmented, electrophoretically homogeneous components showed that these molecules sedimented out much more slowly than serum albumin which is a typical protein.

Sedimentation occurred more slowly because the smaller molecules are acted upon by a lesser force in the ultracentrifugal field.

By correlating the ultracentrifugal data with diffusion studies, it was found that these molecules had molecular weights of about 5,000 each. The main electrophoretically homogeneous molecule in Giant Ragweed solution was named Trifidin; in Dwarf Ragweed solution, Artefolin. A molecular weight of 5,000 is rather low for the molecular weight of a typical protein. Considering the chemical reactions of solutions of these molecules, it appeared that they were not typical proteins. The colorless component of Timothy grass was also studied in the ultracentrifuge but its molecule was so small that it was not sedimented under the conditions of the experiments.

Chemical analysis of the small quantities of these molecules available to the present time, compared with serum diluted 1:30 indicated that these pollen molecules resembled, as far as their chemical properties and molecular weights were concerned, high molecular weight polypeptides rather than proteins. To speak of these allergenic molecules as proteins is more or less fallacious, although they are to a certain extent, protein-like in nature. The name Protoproteins has been suggested for these major colorless components of pollen extracts.^{1,6} The prefix "proto" denotes the first or the lowest in a series. A Proto-protein then, would be a substance on the border line between high molecular weight polypeptides and low molecular weight protein molecules. The designation of these highly allergenic molecules by the term Protoprotein not merely gives them a new name but lends to this new group of molecules an element of predictability. This predictability enables us to state that such small molecules can diffuse more readily and permeate living mucous membranes with greater facility. Also there is greater hope for synthesis in the laboratory. It is of interest to speculate that if the molecular weight of these molecules had been much greater, say one million, the probability of sensitization of the mucous membrane of the respiratory tract would be very much

less indeed, and the facility with which they could be driven into the skin by electrophoresis would be reduced to a considerable extent.

The small molecular weight may account for the rapid onset of anaphylactoid shock following a small overdose of pollen extract.

The administration of pollen extract is, in general not attended with any acute danger or repeated injury to the patient. However, certain recommended procedures increase the dose to just below the level of shock. Indeed, reports of experimentally induced mild anaphylactic shock in patients undergoing therapy is reported with little thought of damage to the patient. Recent experiments by Castberg and Schwartz may indicate a certain degree of laxity in the recommendations often advised for allergic therapy. Castberg and Schwartz⁷ show that in five young hay fever patients following a shocking dose of pollen extracts important changes occurred in the electrocardiograph. In all cases, changes typical for anoxemia of the myocardium were found. Although there was no evidence to suggest any specific allergic reaction in the heart and although the authors believe that the observed changes depend upon decreased ventilation of the lungs, our attitudes in this case should be specifically connected with the welfare of the patient undergoing hay fever therapy. Just what for example, is the effect of overdosage over prolonged periods, for many years? Do doses producing subclinical shock in the tissues lead to chronic changes due to therapy? In view of the fact that this question cannot be answered, it appears desirable at present, to cautiously avoid shocking doses of allergens or doses of allergens beneath the shocking level in the therapy of hay fever and asthma. The local reaction of the patient's skin as well as general reactions are the guide to therapy rather than any particular number of units advocated for a given patient in a routine fashion. The psychological implications in the administration of sub-anaphylactic doses include a threat to the patient by the physician of anaphylactic shock and its consequences. This is unwarranted by any increased value in therapeutic result claimed or attained.

During the past six months by applying a new principle of electrophoretic separation, larger quantities of purified Trifidin, sufficient for clinical trial and chemical analysis are being prepared.⁸ The study of electrophoretically purified material will lead to a better understanding of the relationship between these small allergenic molecules and sensitization.

ANTIHISTAMINIC DRUGS

With few exceptions antihistaminic drugs like Benadryl and Pyribenzamine have aside from their effects on the pharmacologic action of histamine, one very definite characteristic in common: their hypnotic effect. Indeed, the depressant action of these drugs is often so great that patients taking them are cautioned not to use machinery or to drive cars. This is apparently not true to the same extent for barbiturates. Antihistaminic drugs often replace the barbiturates and are frequently given combined with ephedrine. In addition to the depressant effect of the antihistaminic drugs there is also a very definite atropine-like effect which accounts for the drying of the mucous membranes in the therapy of hay fever. When antihistaminic drugs are prescribed in allergic disorders, are we prescribing these drugs to counteract the effect of histamine or are we prescribing them for the hypnotic and atropine-like action combined with a decrease in the permeability of the small blood vessels?⁹

The newer antihistaminic drugs may operate by competing with histamine or similar molecules for the positions within the cells of the tissue. Whether this competitive mechanism is correct or not, the drugs certainly prevent the action of histamine itself under certain circumstances. This antihistaminic action is especially marked with high concentrations of the drug. They should be used with caution in asthma and are often contraindicated because of the atropine-like action. When they are effective in asthma it should be borne in mind that they may be so because of a hypnotic action rather than an antihistaminic effect. In the presence of anxiety, the hypnotic effect of the antihistaminic group is often observed. In spite of value as a hypnotic, the atropine effect is often a reason for contraindication. The atropine effect leads to drying of the mucous membranes, thickening of the secretions, prevention of the clearing of the respiratory tract of mucopurulent materials and therefore interferes with respiration. This is particularly true if the patient has been given other sedatives. The combined pharmacological action of these very powerful depressants with ordinary sedatives is unpredictable on the basis of available data. Another probable contraindication, at present, to the use of antihistaminic drugs, is the presence of infection. There has been a tendency to prescribe these powerful agents independent of the nature of the

illness. Dr. B. S. Halpern of Paris was recently asked at the end of a lecture whether or not, in view of the effect on the capillary permeability of the antihistaminic drugs, there was any influence on the immunologic reactions of the patient. Dr. Halpern pointed out, that although experiments were in progress, the effects on antibody formation were relatively unknown.

It is necessary to recall that there are other drugs which are more truly antihistaminic in their pharmacologic action. Notably amongst these is epinephrine. The antihistaminic effect of epinephrine and other sympathomimetic amines in many times (thousands of times in the case of epinephrine) greater than that of drugs similar to Benadryl and Pyribenzamine. In addition to having an antihistaminic effect, epinephrine also shows the restoration effect.¹⁰ That is, many hours after epinephrine neutralizes histamine in the skin by vasoconstriction (a true pharmacologic antagonism) the epinephrine again may manifest itself by vasoconstriction at the site of histamine action. Similar general reactions were observed first by Cameron¹¹ who found that histamine neutralizes the general effect of epinephrine only in a transient fashion. These observations make unlikely the theory that epinephrine liberates histamine in a quantity of pharmacologic significance.

AEROSOLS

General: The use of aerosol therapy in asthma is not new. Steam inhalations and inhalation of the smoke from burning stramonium leaves are early but still useful examples of aerosol therapy of the bronchi. Many pharmacologically active drugs have been employed. Here the discussion will be limited to ephinephrine and penicillin aerosols produced by oxygen or air pressure. The weight and therefore, the dose of the particle of the drug is proportional to the cube of the radius of the particle. In aerosol therapy of the lungs, therefore, if topical therapy is the therapeutic goal, the results essentially depend upon the dose of the drug delivered to the patient at the site where the dose is to be applied topically.

According to Findeisen,¹² particles of 3 micra and above are taken out completely by the trachea, bronchi, bronchioles and the aveolar ducts. Particles of 1 micron radius and above are removed by the lungs to the extent of 97 per cent with 3 per cent recovered on expiration.

As the radius of a particle gets smaller, particles of 0.3 micron radius are absorbed to the extent of only 35 per cent with 65 per cent recovery on expiration. These conclusions of Findeisen are confirmed by the experimental work of van Wijk and Patterson¹³ who showed that solid particulate material of 0.6 micron radius was removed to the extent of 63 per cent while particles ranging from 0.6 micron radius to 2.0 micra radius were removed from 63 per cent to 96 per cent. Particles less than 0.4 micron in radius were retained to the extent of about 30 per cent. All of these data support the point of view that rebreathing equipment is unnecessary in routine aerosol therapy. With a suitable nebulizer and the proper technique of having the aerosol inspired with the initial phase of inspiration, excellent therapeutic results have been obtained by direct inspiration of the aerosol from the nebulizer without a rebreathing bag or other complicating equipment.^{14,15}

Epinephrine: One of the most useful methods of treating asthma is by the nebulization of a 1:100 epinephrine salt solution provided that certain conditions are fulfilled:¹⁶

1. The droplets are stable and do not evaporate rapidly.
2. Therapeutically suitable particle size distribution is achieved.
3. Nebulizer delivery is adequate.

There are many different types of nebulizers available commercially. These are reviewed in an interesting and excellent article by Harsh.¹⁷ Added to the nebulizers enumerated by Harsh should also be mentioned as meritorious a double jet nebulizer made available recently.

This double jet nebulizer has many interesting features and is worthy of further investigation in aerosol therapy. In general, ordinarily commercially available solutions of epinephrine, evaporate too rapidly on leaving the nebulizer. A vertical nebulizer is preferred since a horizontal nebulizer increases the danger of swallowing the solution. Certain nebulizers, horizontal in construction, however, deliver excellent mists and are suitable if the patient is careful. Once the nebulizer has been chosen it is important that the nebulizer operates efficiently with the solution employed. In spite of the fact that 1:100 epinephrine solutions appear with various names as pointed out by Harsh, the important feature of all of the solutions is the fact that they contain about 1 per cent biologically active epinephrine. Other sympathomimetic amines related to epinephrine are also available for nebulization but

whether they are as suitable as epinephrine for nebulization therapy in asthma is still a matter for further clinical study.

It is important to instruct the patient that the nebulizer performs satisfactorily only when delivering a fairly stable, visible, dry, mist. The stability of the mist is critical because if the particle size is not correct, evaporation of the particles occurs and effective deposition of the epinephrine droplets in the lungs may not occur. In order to stabilize the epinephrine solution, at least 10 per cent of glycerine is desirable. U. S. Army Stock Item No. 1,175,320, July 16, 1945, employs 25 per cent of glycerine. I believe that this concentration of glycerine is a suitable stabilizing agent and is better than the 50 per cent of glycerine which I recommended in 1940.¹⁶ The presence of 25 per cent of glycerine prevents rapid evaporation of the particles and thus gives a particle size suitable for therapy. This concentration of glycerine brings aerosol therapy with epinephrine into an area of optimal predictability. The difficulties encountered often arise because of the lack of predictability in both nebulizer and solution, each of which contains variables which are not controlled. The favorable clinical experiences with approximately 25 per cent of glycerine are borne out by the experimental work of Bryson, Demerec, Laskin and Potter (Seventh Monthly Progress Report to Contract No. 266, CWS 246 between the War Department and the Long Island Biological Association Inc., October 10, 1943), who showed glycerine aerosols of the greatest persistency are achieved with solutions containing 30 per cent of glycerine. A plateau is maintained with glycerine concentrations up to 70 per cent but optimal values were obtained at 30 per cent. This confirms clinical observation that about 25 per cent of glycerine gives the optimal predictability for aerosol therapy with epinephrine solutions. Most cases of mild to moderate asthma uncomplicated by other factors (e.g. anxiety neurosis) are readily controlled by aerosol therapy with stabilized epinephrine solutions.

Epinephrine salt solutions should preferably be between pH 4 and 5. This is readily obtained by titrating 1 gram of epinephrine base with approximately 5.2 cc. of molar phosphoric acid and diluting to 100 cc.

Failures with this type of therapy may usually be traced back to:

1. Insufficient solution being used in the nebulizer.
2. A poorly constructed nebulizer.
3. Insufficient glycerine or other stabilizing substance.

4. An excessive amount of secretion in the bronchial tubes preventing access of the aerosol to the points required.

5. An emotional state of the patient, e.g., anxiety¹⁸ in which sympathomimetic amines are essentially contraindicated except in very small doses. Very often patients in an anxiety state are called "epinephrine fast." The epinephrine "fastness" of these patients is not always due to the fact that epinephrine has been employed. Indeed, "epinephrine fastness" can be observed in several categories:

- a. When epinephrine has not been used for some time.
- b. When only a small amount of epinephrine has been administered.
- c. When a considerable amount has been administered.

In view of the fact that "epinephrine fastness" can occur when there has been no opportunity for a true pharmacologic tolerance to be achieved as under a, and b, it is important that the emotional state of the patient be considered. Epinephrine should never be administered if it is not obviously effective. If ephedrine derivatives by mouth are not satisfactory, the patient should be instructed to use epinephrine aerosol wherever possible to prevent an impending attack. In this way, the excellent results obtained with epinephrine aerosol therapy justify the statement that in most instances inhalation can replace injection.

Still commonly used are aerosols formed by burning stramonium leaves. These aerosols may be obtained by either burning the powder on a small dish or by smoking stramonium cigarettes. The clinical effectiveness of these smokes is presumably due to the presence of stramonium. However, the active biological agents in these aerosols have not been chemically isolated and identified.

Clinical data are available on other aerosols: aminophylline, theophylline, atropine as well as substances similar to epinephrine itself.

Penicillin.^{14, 15, 19} Penicillin aerosol is indicated in the therapy of asthma if it is believed that penicillin susceptible organisms may be present and if the presence of these organisms is producing an infection which requires antibiotic therapy. This is true independent of the origin of the asthma. The asthma may be produced by allergenic molecules such as pollen with secondary infection, by bronchiectatic processes or by other types of lesions leading to secondary infection of the lungs. The administration of penicillin in cases of this type should not be restricted to its use in aerosols. Simultaneously, injection of the antibiotic should be carried out. In addition, penicillin aerosol therapy

should be preceded by an aerosol of epinephrine 1:100 to reduce narrowing of the bronchial tubes. As far as the concentration of the penicillin is concerned in the aerosol, the main error is administering too small a dose and concentration. Aerosols are preferred with concentrations of penicillin of at least 200,000 units per cc. with the oxygen flow about 6 liters per minute by mouth or at 10 liters per minute if nasal tips are employed. It should be ascertained if the nebulizer employed functions efficiently at 10 liters flow per minute. The minimum of 50,000 units per cc. with oxygen at 6 liters per minute 2 or 3 times daily is permissible. Preferred, is at least 500,000 units administered in 2 cc. at least twice daily with nasal tips, if possible. Certain commercially available nebulizers are adapted for these procedures. The details^{14, 15, 17} may be found elsewhere but the output at 10 liters per minute should be confirmed by checking the delivery of the nebulizer by standard dyes.²⁰

The recent commercial introduction of penicillin dust brings up an important point. The mean particle size of one of these dusts²¹ is so large that only a small fraction of the dose is in small particles. If the therapeutic claims are justified, and this requires further evidence, how can we explain the therapeutic results, assuming them to be correct? Is the theory concerning particle size distribution incorrect or do we have an unexpected and new technique? If we examine the fate of Lipiodol, which can be atomized into the lungs employing a DeVilbiss atomizer (No. 152) a bronchogram is obtained following the deposition of the Lipiodol in the trachea and bronchi.

The same thing might occur, although this has not been definitely proven, when large particles of the penicillin dust are breathed in through the mouth. A certain fraction of the large particles may pass the larynx and adhere to the trachea and bronchi. The penicillin may then through gravitational forces pass to one side or the other of the respiratory tract, depending upon the position of the patient in the same way as that depicted for Lipiodol. It does not appear likely that penicillin dust of this type can supplant aerosol therapy with the nebulizer. The particle size distribution is very different, indeed. Judging by what has been covered in regard to the particle size distribution in the lungs it is inconceivable that the same distribution can be achieved with large particles that can be obtained with small particles. In the case of small particles, the particles are fairly uniformly distributed throughout

the bronchial tree by the force of the convection current of inspired air. In general, according to theory and experiments, deposition of large particles must occur in the upper part of the bronchial tree with partial drainage to the lower part of the bronchial tree dependent upon accidental factors, especially gravity.²²

It is pertinent to the mechanics of the therapeutic effects of aerosols comprised of either liquid or solid particles to know that as the particles are floated in the air through the bronchial tree some material will be deposited whenever a corner is turned by the aerosol. For example, as the aerosol turns a corner about a purulent deposit, some of the aerosol is deposited on that part of plug facing the aerosol flow. This can be shown experimentally with dyes.

If a minute mass of gelatin or agar is placed in a glass tube and an aerosol of a red dye is passed through the tube, deposition of the dye on the side facing the flow of the aerosol is readily observed. This apparently insures automatic deposition on purulent material in the line of flow. This phenomenon can also be seen following the administration of phenolsulfonphthalein aerosols to patients with lung infections. The mucopurulent material coughed up is often mainly colored on one side with the dye diffusing toward the other part of the material. In all likelihood, penicillin aerosol deposits in the same way in the respiratory tract wherever corners are turned for mechanical reasons of any kind.¹⁵

NARCOTICS

In spite of the fact that asthma is a chronic disease with a comparatively long life expectancy, narcotic drugs known to be habit forming and coming within the scope of our narcotic laws are still being widely used. An extreme example of this, was a recommendation to the daughter of a patient whom I saw in consultation, that the daughter, as a nurse, could administer morphine intravenously to her 75 year old mother in status asthmaticus. What the pharmacologic reason was behind this suggestion is puzzling since morphine often causes death in patients of this age. There does not seem to be much diversity of opinion that morphine is contraindicated in asthma not only because of its depressant effect but also because of the probability of habituation. Related drugs like meperidine hydrochloride (Demerol) also come under the narcotic laws. These drugs are also respiratory depressants.

Therefore, Demerol and similar substances are contraindicated in older patients because of their depressant action and should not be prescribed for younger individuals because of the danger of habituation. The serious consequences of addiction cannot be disregarded. The anxious patient who requires quieting can be treated by ways other than those provided by habit forming narcotics. If the therapy of asthma depends upon habit forming narcotics then psychotherapy is indicated.

PSYCHODYNAMIC PHARMACOLOGY AND THE THERAPY OF ASTHMA

Although the respiratory difficulties under discussion have a basic etiologic structure, immunologic in nature, the intensity and persistence of asthma is maintained in many patients because of the presence of unconscious conflicts which lead to difficulties in the conscious, realistic realm.²³ The nature of these conflicts in allergic individuals has been in part determined by psychoanalysis. It is well for us to clarify the relationship by what is learned by psychoanalytic procedures to the practical therapy of the asthmatic patient. While it is desirable, and indeed essential for the physician to understand the relationship of unconscious conflicts to the origin of asthma, the material obtained by psychoanalysis should not be the subject of direct discussion by the physician and patient. I mention this because publicity in the daily press has recently been given to unconscious material derived from psychoanalytic studies of asthmatic individuals. It is questionable if the asthmatic person should be suddenly confronted with unconscious material of this type in press reports. Certainly the well trained analyst would consider this in actual practice as one of the gravest of technical errors.

To illustrate what is meant by the unconscious, may I utilize an analogy. There are here in New York City, two methods of projecting motion pictures. The type most commonly used is that in which the light is passed over the heads of the audience onto a reflecting screen. Portrayed on the screen is a realistic pattern of activity readily observed by the audience. The origin of this pattern is easily traced back to the projector which throws these realistic images on the screen. These images on the screen correspond to the clinical manifestations of the patient which are accessible and observable. The second type of motion picture projection is commonly found in newsreel theatres. In this type the same activity is readily visible on the screen but there is no orienting beam of light to be traced back to the projector. The screen in this case

is both reflecting and transparent. But the projector is invisible and is situated behind the screen. There is no way of immediately deriving from the realistic activities on the screen, the hidden mechanisms embodied behind the screen in the projector. The unconscious mechanisms of the patient are just as hidden from the physician, perhaps more so, than the projector in the newsreel theatres where the projector and the sound track are behind a screen and not available to the observer of the screen except by passing to the area behind the screen. The procedure of psychoanalysis elicits unconscious material by determining in part the psychodynamic mechanisms which result in realistic activities observable to the physician. Although it is necessary to recognize that mechanisms behind the screen of conscious activities of the patient determine his symptoms and complaints, it is usually difficult to utilize them directly in the treatment of the acutely ill asthmatic patient. We should be more concerned with recognizing the general psychologic pattern by means of which he deals with his inner stresses, in conjunction with utilizing the action of drugs in an explicit relationship to the immediate, dominant emotional state of the patient. It is necessary, therefore, to recognize and to utilize the *psychodynamic pharmacology* of drugs like epinephrine, the barbiturates, etc, used in the treatment of asthma.

It was first shown by Eduardo Weiss²⁴ and by French and Alexander²⁵ and their group as well as by others, that the outstanding psychodynamic process in the asthmatic patient is the unconscious fear of the loss of the mother or mother image or parent figure. These unconscious psychomotive forces, developed early in the life history of the patient, are modified and diverted by the psychological, physical and cultural growth of the patient, with this fundamental and unconscious pattern of anxiety however, persisting. The intrusion of other psychomotive forces may change the syndrome observed in asthma so that the patient almost always presents a mixed syndrome with certain features outstanding. In the following brief and schematic classification of asthmatic patients, the dominant affective tone which the patient exhibits is taken as the guide to therapy and pharmacologic measures should be initially adapted to the impression made after studying the patient as a whole. Often the drug administered will intensify the neurotic pattern and thus confirm the diagnosis by increasing the severity of the symptoms. With this concept in mind

some additional aspects of psychodynamic pharmacology of the therapy of asthma will be outlined.

*The Anxious Asthmatic Patient.*²⁶ An undercurrent of anxiety characteristic of chronic disease is especially prominent in all cases of bronchial asthma. Interference with breathing is always a threat to life. This is well emphasized by the frequent occurrence of psychoneuroses following minor gas injuries especially noted in World War I and in industrial accidents at the present time. Another instance which illustrates the special attitude toward lung injuries was that of volunteers in the last war toward experimental production of mustard burns. Volunteers were readily obtained for experimental skin lesions but great reluctance was encountered when inhalation experiments were suggested even though reassurance was given that no permanent injury would result.²⁷ This undercurrent of anxiety may become a dangerous undertow in the asthmatic patient. The danger lies not only in the immunologic and psychologic realms but also in overtreatment by the physician. Indeed, it is well recognized amongst allergists that many cases of bronchial asthma are subjected to pharmacologic traumata, where the drug intensifies the symptoms because of the mental state of the patient. If we accept the point of view that an undercurrent of anxiety exists, practically speaking, in all cases of asthma, it is important to search for symptoms connected with anxiety. For example, in taking the history it is necessary to ascertain if the asthmatic attacks started by difficulty on inspiration or difficulty on expiration. The respiratory cycle, in many cases, must be carefully explained to the patient. However, after the patient understands the respiratory cycle, instead of saying that the attack was asthma, the statement may be made that there was difficulty getting air in or in catching the breath. Difficulty in catching the breath or in getting the breath is not equivalent to a classical attack of asthma. In classical asthma of course, the difficulty is on expiration. If there is difficulty on inspiration, and especially if the attack of asthma begins with difficulty on inspiration, it is wise to administer, in very small doses, epinephrine, whether by injection or inhalation, or, ephedrine and related substances orally. This is necessary because epinephrine itself is apt to produce anxiety in larger doses.^{11,18} Very often difficulty on inspiration develops into a mixed syndrome with difficulty on expiration dominating the picture. The underlying anxiety is just as important a part of the pattern that has to be treated as the difficulty

on expiration which under ordinary circumstances responds to the sympathomimetic amines.

Another aid in determining the degree of anxiety is by observation of the patient's oxygenation. If the action of the chest muscles is great and the color is good nevertheless, it may be desirable to use oxygen with the understanding that the response to oxygen in a case of this type may be more of a test for an underlying neurosis than an active therapeutic procedure embodying pharmacologic action. Patients of this type often respond almost immediately to oxygen. Indeed, it is frequent to have a patient claim relief within one minute after having the tube with oxygen passing through it, placed in the mouth. Sometimes, relaxation follows merely placing the tube in the mouth even before the oxygen starts to flow. Anxious patients may often refuse to go into the oxygen tent or wear an oxygen mask. This anxiety is important because it reflects a phobic component in the patient's make-up. The use of sedation in patients with anxiety is usually indicated. Chloral hydrate with or without the barbiturates is very effective. There is no routine dosage. The dosage depends upon the pharmacologic response of the patient as well as his character structure. This is of importance in certain cases where sedation leads to regression to an infantile level, thus decreasing the coöperation and increasing the infantile behavior.²³ The predominantly anxious type will often speak of dying during the attack. Reassurance is desirable, even if the patient himself does not suggest the possibility of death. It is always wise to make certain that the patient understands that asthma is a chronic disease that can be prevented from becoming serious if he coöperates with the physician.

The Depressed Asthmatic Patient. In certain cases the asthmatic patient is found to be an ostensibly submissive and obedient patient. His submissiveness and obedience very often are a reflection of a depressed attitude. In these patients it is very wise to study the effects of sedation which may under certain circumstances, be contraindicated because of the effect on the depression itself. The depressed patient will very often prefer to have epinephrine by injection rather than by the nebulizer because of the stimulating effect of the injected epinephrine. Very often the depressed patient will say that he feels better after an injection of epinephrine even though the severity of asthma has hardly changed. The depression should be treated cautiously as with other depressed states by the administration of small doses of amphetamine sulphate,

period of years, the vital capacity was unchanged by the administration of epinephrine aerosol but there was definite relief of the feeling of restricted motion in breathing. The epinephrine aerosol produced no change in the chest signs. Apparently the reassurance given by the nebulizer in the mouth plus a small dose of a sympathomimetic amine resulted in improvement in the feeling of the constriction of the chest. This patient, who has refused psychotherapy, has used epinephrine aerosol for many years to relieve what she considers to be asthma but which really is a feeling of constriction in the chest which most often occurs without any signs or symptoms of asthma but with feelings of anxiety. In order to avoid any misunderstanding in regard to the psychotherapy of the asthmatic patient, it should be noted that I believe that for the best results psychotherapy should be in charge of an allergist with suitable psychiatric training or of a psychiatrist with an understanding of the immunological aspects of asthma. It is not intended that the writer anywhere implies that unconscious material should be casually employed, or that the general practitioner should utilize techniques of deep psychotherapy.

May I now summarize how the use of powerful sympathomimetic amines, antihistaminic drugs, sedatives and antibiotics in the treatment of bronchial asthma should be oriented. While it is generally agreed that therapy should not neglect the physiology and the immunology of the patient in the asthmatic state, the personality of the patient cannot be omitted in planning suitable therapeutic procedures. It is neither wise nor desirable for the patient suffering from severe asthma to be reminded of unconscious material that the doctor himself may be aware of. It is more than desirable in our present state of knowledge to use pharmacologically active drugs in connection with the total personality of the patient manifested during the acute asthmatic attack. Whether anxiety, phobia, depression, dependence, hostility, grief, or other pattern dominates the asthmatic attack, the physician should bring into the proper sphere the psychodynamic pharmacology of the drug employed in treating both the asthmatic spasm and the personality of the patient himself. In this way a better understanding of the action of the drugs on the personality of the patient will be obtained with much greater predictability in the therapy of bronchial asthma.

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MEDICINE UNDER MUSSOLINI*

MARIO VOLTERRA

I IN THESE uneasy times in which we are living it is proper and—let us hope—useful to look back at the past for guidance and inspiration. We agree with the organizers of these meetings of the Historical Section of The New York Academy of Medicine, that history includes not only ancient times, the Renaissance, or the triumphal era of scientific and medical progress of the 18th and 19th centuries, but also the years just past. With this idea in mind I was asked to trace the influence of a dictatorial, totalitarian regime on medicine and medical education in Italy. I wish to express my gratitude for having been given this opportunity.

It is my intention to present an objective report giving proper stress to both the bad and the good developments in Italian medicine from 1922 to 1943, the period of the fascist regime. I will tell you right now that the balance will not turn in favor of that regime, which unfortunately did not fail now and then to get some praise even from some democratic countries.

In order to have the proper perspective it is necessary to recapitulate very briefly what Italian medicine represented and contributed during the last century and what its situation had become in the 1920's. I shall recall to you a few of the names connected with important medical developments, trusting that the majority of them will be familiar to you.

The brilliant tradition in anatomical studies which reached its highest point with Morgagni (1682-1771) was maintained during the 19th century by Scarpa, Corti, Pacini, and at the end of the century by Golgi. Golgi's contribution was twofold. His researches in neuro-anatomy were recognized by the award of the 1906 Nobel Prize conjointly to him and to Ramon y Cajal. His research on malaria is also of high importance. In the field of pathology and pathological anatomy

* Presented before the Section on Historical and Cultural Medicine of The New York Academy of Medicine, 12 November, 1947.

there were two world-famous men: Banti, who is remembered for his work on the spleen and on hemolysis, and Marchiafava, who contributed fundamental studies on malaria and later described paroxysmal nocturnal hemoglobinuria with hemosiderinuria, also known as the Marchiafava-Micheli Disease. In the spring of 1901, when Harvey Cushing was working on the relations between intracranial pressure and blood pressure he went to the laboratory of Angelo Mosso, the Turin physiologist, to complete his research. Among well known medical men let me mention Forlanini, whose fame is connected, as you know, with the discovery and clinical application of therapeutic pneumothorax in tuberculosis, and among the surgeons Bassini, who developed the first rational operation for hernia. To this list of medical men I like to add Cesare Lombroso, the criminologist, and the zoologist Grassi, who discovered the role of mosquitoes in the transmission of malaria.* I beg you to consider that these few men were able to achieve universal fame through the sheer value of their work. They spoke and published in a language which is comparatively unknown outside the boundaries of their own country, a country which has little political weight and which is thought of generally, though unjustly, as being rich only in natural beauties and artistic tendencies but poor in scientific achievements. And these men were, all of them, modest and even shy. They were men who did not come out of their universities to cultivate international contacts.

These men are mentioned here because their fame spread beyond the confines of their country, but others should be added who worked in every field of medical research and whose names are found when one looks diligently through the literature. Some of these were famous teachers who had a powerful influence in molding the minds of several generations of good doctors, at a time when the personality of a teacher not rarely had the power of leaving a permanent imprint on the intellect and character of the student.

The doctors who were educated in the medical schools of Italy in the late 19th century were for the greater part good general practitioners, well schooled in the art of questioning patients and examining them with the most minute resources of a painstaking physical examination. They were, of course, poorly provided with effective means of treatment. They were modest and honest, and—I gather—not dissimilar

* The Nobel Prize for this discovery went to Ross, who demonstrated the infection of birds by means of the mosquito but it was Grassi who proved experimentally that malaria is transmitted to man by infected mosquitoes.

to the doctors of France or Austria, of Great Britain or the United States.

In the first two decades of the 20th century the picture started to change. Although some of the men to whom I have referred were still active as research workers or teachers and although their schools still produced new generations of young scientists and clinicians, it seemed as if a strange debilitating process had set in which was progressively reducing the productivity of these institutes and clinics, as far as quality is concerned. Looking at this process now, retrospectively, it seems to me that the explanation of this unhappy event may be found, at least in part, in the progressively extending gap between the material set-up of Italian medical institutes and the increasing technical complexity of medical research and teaching. Until the end of the First World War the great majority of the medical university institutes in Italy were located in old quarters, badly cut up from ancient and antiquated hospitals or monasteries. These establishments were usually deficient in technical facilities such as hot water, steam, and vacuum. Very often they even lacked a sufficient heating system. What is still more important, they operated with a ridiculously low annual budget which included reagents, animals, gas, electricity and even salaries of technical personnel. To sum up, the equipment of the institutes and clinics had not changed essentially from that which had prevailed in the previous century, at the time when medicine was only emerging from the field of simple—and inexpensive—speculation.

With the increasing complexity of biological and medical problems another insufficiency of this system became more and more acute. In order to achieve some success in modern medical investigation a certain amount of team work is almost always necessary. Even for efficient teaching the help of a large staff of well-prepared assistants is indispensable. The choice and training of good assistants is, of course, primarily the responsibility of the chief of the institute, but his task cannot be carried out if the conditions under which the assistants are supposed to work are such as to make their life financially insecure and spiritually unsatisfactory. During the period when medical research was essentially morphological and clinical teaching was predominantly theoretic—as was the case until the first decades of this century—the lack of laboratory facilities and the insufficiency of the staff was not felt. These factors did not prevent the Italian medical schools from

participating actively and with honor in the scientific arena and did not prevent them from preparing good medical men capable of practicing medicine according to the standards of the time. But when medical research became increasingly based upon physiological, chemical, and immunological foundations, with the accompanying expensive technical paraphernalia, the newer generations of investigators were hampered more and more in their work. Medical teaching became stale and medical practice antiquated. It is really remarkable, and a proof of the perseverance and spirit of these workers, that several Italian medical schools were able to maintain medical research at all and were even able to produce some prominent men, such as Micheli, the clinician of Turin; Ferrata, the hematologist of Pavia; Putti, the orthopedic surgeon of Bologna; Cerletti, the neurologist of Rome, the originator of electro-shock; G. Levi, the histologist of Turin.

This was the situation prevailing at the end of the First World War. Among the many problems of reconstruction and modernization which faced Italy, some of the most urgent were the reform of higher education, the modernization of health administration, and the rejuvenation of medical practice.

In Italy fascism was born and was triumphant in the fall of 1922. The effect of its policy upon medicine was gradual and started to make itself apparent only around 1925. Let us recall a few of the most important developments.

In the general reorganization of the universities, which was a part of the reform executed by the Minister of Education, Giovanni Gentile, the medical schools, which were eighteen in number, were increased to twenty through the creation of the medical faculties of the two new universities of Bari and Milan. Meanwhile, new plans were made and the old ones pushed forward for the construction of new institutes and clinics. These were gradually completed during the space of some ten years. In this way new buildings were erected in Milan, Parma, Florence, Siena, Rome, Perugia, Cagliari, and Sassari. It is to be regretted, however, that while these new buildings were provided with completely modern facades and designed with that architectural good taste which makes pleasant the look of so many Italian public buildings, the internal arrangement of these institutes very often did not include many of the modern facilities and appliances which are necessary today for research and even for routine

work. The interest of the planners and the money of the State were dedicated to outward appearance rather than to the provision of implements for working. There is no doubt in my mind that the reasons for these incongruities were several: first and foremost, that love for appearance, which not rarely amounted only to bluff, that was characteristic of the fascist regime in every field; second, the fundamental lack of understanding of the needs of serious research, and even of its usefulness and importance among national activities, which was also typical of the fascist mentality; and third, the vanity of the planners, both architects and chiefs of the institutes, who were willing to sacrifice good work for good looks. This regrettable tendency was encouraged by the very simple method of allotting relatively large sums for the construction of new buildings and little or none for equipment. Moreover, the old annual budget destined for the maintenance and operation of the institutes was not increased or at least not greatly enough to permit a change from the inefficiency which had prevailed in previous decades.

In spite of all of the claims of the government that the fostering of the national culture and the increase of its international prestige was among its first aims, nothing was done to improve the spiritual and material condition of the university personnel. The National Association of University Assistants, a progressive body which had emerged after the First World War as the spokesman of the university staffs, was very soon taken over by the fascists, purged of all its liberal elements, and transformed into an organization of political vigilance. In this way the university assistants found themselves enclosed in a net of espionage which threatened their present and their future. Do not forget that in Italy the universities belong to the State and the future of the career of any assistant or professor is in the hands of the State. It was only because fascism had great difficulty in destroying the spirit of independence of the old class of professors, that for several years political pressure did not influence their judgments in the nomination of the new professors. But after 1932 the resistance of the ranks of old professors had started to dissolve and conformity, or at any rate passive obedience, was required from everyone in a university career. In 1931 an oath of allegiance to the regime was decreed and requested from every university employee, professors included. In 1932 proof of membership in the fascist party was made obligatory for those who

wished to become full professors, just as the birth certificate, the criminal record, and the documentation of teaching activity were required. The alternative was disruption of the university career. For many men this involved the loss of their only source of income, not to speak of the political persecution which was to be expected as a consequence of what amounted to an act of rebellion.

Since the percentage of convinced fascists was very small and since everyone knew this, the obligation to take the fascist oath and the inscription in the fascist party against one's own convictions were great humiliations and certainly resulted in no increased morale among the members of a class which can hardly keep its prestige after the loss of self-respect.

Although a reform of instruction was one of the first important acts of the new regime, this reform affected the secondary schools mostly and failed to change the methods of teaching in medical schools. Medical teaching remained theoretical and consisted of amphitheatre lectures, even in clinical courses. Practical exercises were also in the curriculum but were usually restricted to a few hours a week and moreover were severely handicapped by the large number of students and the scarcity of facilities. Since the conduct of laboratory exercises and clinical seminars falls on the shoulders of the assistants, and these men, as I have said, were dissatisfied, the practical teaching of medicine did not improve. The way in which doctors were prepared for their profession during the fascist regime was not different from that which had prevailed before.

While this was the picture as far as undergraduate teaching was concerned, very little opportunity was offered by the medical schools for postgraduate education, and none for keeping the practicing physicians up-to-date. The only postgraduate education available was that open to a few men who had special financial resources and could remain in the university institutes for several years after graduation. Such men acted as assistant professors. In this way the title of "*libero docente*" was acquired, corresponding to the German "*Privatdozent*" and to the French "*agregé*." This title, however, was usually desired as a means of acquiring a better practice. The institution of free teaching, which is characteristic of continental universities and which is capable of rendering good service in medical education, was not substantially improved by the fascist reform. Well-organized refresher

courses for medical practitioners were lacking, as before; no effort was made to extend to these practitioners the opportunities offered by the educational mechanism of the universities.

While the governmental program, which consisted of the erection of new buildings and new clinics, was unable to change Italian medicine as far as scientific research and medical education were concerned—for reasons which I have attempted to indicate—it had some effect in the field of public health, where with an eye to political advantage, efforts were directed not only toward the expansion of buildings but also toward lengthening the rosters of government employees. Two gigantic problems of public health have always defied the action of every government in Italy. These are tuberculosis and malaria. Mortality from tuberculosis was 154 per 100,000 inhabitants in 1924. Malaria prevails in Italy only in a few comparatively limited coastal areas and in the two islands of Sicily and Sardinia. Although this disease presented no great problem from the point of view of mortality—there were only 4,000 deaths from malaria in 1924—it presented a considerable problem in terms of morbidity and economic losses. Thus there were 251,000 reported cases of malaria in 1924 alone.

The fight against tuberculosis was conducted along several lines. With the construction of new sanatoria and specialized hospitals the number of the beds available for tuberculosis patients, only 13,800 in 1935, was increased to 51,300 in 1940. Campaigns for the dissemination of elementary knowledge of this disease among the laity were conducted every year. Children and young people, being especially vulnerable, were sent to marine colonies and mountain camps every summer. All these measures, but particularly the last, which used to impress even foreign observers, were really effective. By 1940 the Italian mortality from tuberculosis had been reduced to 75 per 100,000, which was not much above the 1930 level of the United States (70 per 100,000).

Malaria was also attacked simultaneously from different angles, as it should be. Antilarval campaigns were intensified, the reclamation of coastal swamps was conducted on a very large scale, the organization of antimalarial stations, which still remained far from perfect, was improved. An Institute of Malariology was created in Rome, where it would do good work because it could use the collaboration of the excellent malariologists with which Rome has always been well pro-

vided since the times of Baccelli, Grassi, Celli, Marchiafava, and Bastianelli. In this work the Rockefeller Foundation was of great help. Mortality from malaria was reduced to 1.7 per 100,000 inhabitants, or only 750 deaths for the whole country. Morbidity was brought down to 61,000 cases, one-fourth the 1924 figure.

A part of the results obtained in these large fields of public health was due to the coördinated activities of organizations such as the Central Institute for Health, annexed by the Ministry of the Interior in Rome as a research and teaching center, and the National Fund for Maternal and Child Care (*Opera Nazionale per la Maternità ed Infanzia*). This National Fund for Maternal and Child Care was already planned when the fascists took over. It was developed during the regime of the fascists, who took all the credit. It still operates in the new Italian Republic of today. Its work was certainly important in helping to reduce infant mortality, possibly because it was effective in the fight against tuberculosis.

This is about all I can say in the short time that I have at my disposal about medicine in Italy under Fascism. A more complete analysis, garnished with more statistical data, would not change the general picture. And this is a sad panorama, dominated by a substantial contrast between claims of progress, for which the regime wanted the entire credit, and actual inertia—except, as I pointed out, in the field of public health.

Now it is proper to ask whether the credit for the work of rehabilitation in such a large field of public health as the fight against tuberculosis and malaria should go completely to fascism or whether it should not go also to those who conducted the campaign at the periphery, i.e., the doctors, the welfare associations, the volunteer workers, and so on. As I saw this job done, being in the midst of it from 1924 to 1938 in different capacities from that of a country doctor to that of a university professor, the work was done for the greatest part not for political reasons, fascist or otherwise. It represented the honest contribution of citizens willing to better conditions for the general welfare of their country. It proceeded from the devotion of the people to the cause of their fellows' betterment. It was also a response to a call of duty untinged by political ideology.

As a matter of fact, when the regime and its propagandists were proclaiming that infant mortality should be decreased and maternal

SECTION ON MICROBIOLOGY

JANUARY 19, 1949

I. EXECUTIVE SESSION

Reading of the Minutes

II. PAPERS OF THE EVENING

INSECTICIDES

a. Chemical aspects of some of the newer insecticides

H. L. Haller (by invitation)
U. S. Department of Agriculture
Washington, D. C.

GREGORY SIIWARTZMAN
Chairman

b. The major toxic actions of insecticides

A. J. Lehman (by invitation)
Federal Security Agency, Food
and Drug Administration,
Washington, D. C.

c. Recent advances in medical and veterinary entomology

E. F. Knipling (by invitation)
U. S. Department of Agriculture
Washington, D. C.

HARRY MOST
Secretary

Chemical Aspects of Some of the Newer Insecticides

H. L. HALLER

The use of chemicals to control injurious insects has been accorded more publicity during the past five years than in all the previous years during which research on insecticides has been carried out. This attention has been due in a large measure to the discovery of the outstanding insecticidal properties of several synthetic organic compounds, especially chlorinated hydrocarbons, such as DDT, benzene hexachloride, chlordane, and toxaphene (chlorinated camphene). More recently several organic phosphorus compounds have been found to be highly toxic to a wide range of insects. Several of the discoveries were made at a time when the need for better insecticides to control insect pests on food and fiber crops, stored products, livestock, and forest products was greater than ever before and when the available supply of the standard agricultural and household insecticides—pyrethrum, nicotine, rotenone, and the ar-

senicals—was unusually low. Although the findings may appear to some to be due to hastily initiated wartime research and largely fortuitous, this is not the case. Rather, the discoveries are the culmination of extensive explorations over a period of about 80 years. Chemicals have been used for a longer time to combat injurious insects but it is only since about 1867 that a systematic study to find new insecticides has been under way.

The early studies were concerned largely with inorganic compounds such as paris green and lead arsenate. By 1910 agricultural practices had become more intensified and insect populations increased, as did the losses which they caused to many important crops. About the same time investigators became interested in finding out how insecticides kill, and emphasized the importance of their physical characteristics, such as wetting and spreading of sprays, on

foliage and insects. A few years later studies were initiated to determine the chemical structures of the highly effective, naturally occurring plant insecticides, the pyrethrins and rotenone. These studies proved fruitful, and the structural formulas that were developed served as patterns for the preparation of organic compounds thought to be toxic to injurious insects. The studies were supplemented by the testing of a large number of synthetic organic compounds which became available soon after the first World War and for which a use was being sought. The two approaches have been profitable and have led to the discovery of a number of compounds highly toxic to insect pests.

The knowledge that an organic compound is highly toxic to several species of insects is not the only requirement for its immediate widescale use. Before its utility in controlling injurious insects can be determined, information must be obtained as to the safety of the chemical to public health, to farm animals, to soils, to vegetation, to beneficial insects including bees, and to wildlife wherever these interests are involved. It is necessary to know the range of effectiveness (that is, to what kinds of insects the product is toxic); the stage of the insect that is destroyed (egg, larva, or adult). Such studies are the joint affair of biologists and chemists.

Few, if any, of the newer insecticidal chemicals are suitable for use as insecticides in the undiluted form. Aside from the fact that it would be uneconomical for most purposes to use potent agents without diluting them greatly, the physical properties of the substances usually are such that they are unsuited for direct application. To determine whether the compound can best be applied as a dust, spray, or as an aerosol a knowledge of the physical and chemical characteristics of the product is needed. Physical and chemical studies should include determination of the composition of the product, its solubility in various solvents, and its compatibility with other insecticides, fungicides, and dust diluents. Methods for the analysis of the product itself, as well as in dusts, in sprays, and in combination with other insecticides, must

be developed. Procedures for determining the product as a spray residue are also needed.

As the time allotted to me will not permit the discussion of all of the newer insecticides I shall confine my talk to the chemistry of some of the more important chlorinated hydrocarbons and the organic phosphorus compounds.

The chlorinated hydrocarbons that have attracted most attention are DDT, TDE (also known as DDD), methoxychlor (methoxy analog of DDT), benzene hexachloride, toxaphene (chlorinated camphene), and chlordane. Although methoxychlor contains oxygen it is included because of its close relationship to DDT. The technical grades of all six of these products are mixtures of two or more isomeric compounds, the relative insecticidal value of which varies with the product and the test insect. The empirical formula and the total chlorine content of each is given in Table I.

These products possess one common chemical characteristic to which their outstanding insecticidal property has been attributed. In the presence of alcoholic alkali and in some cases with traces of certain metals, such as iron, aluminum and others they lose one or more moles of hydrogen chloride. If this reaction is a factor in making them toxic to insects it is only a minor one as many related compounds are known which likewise yield

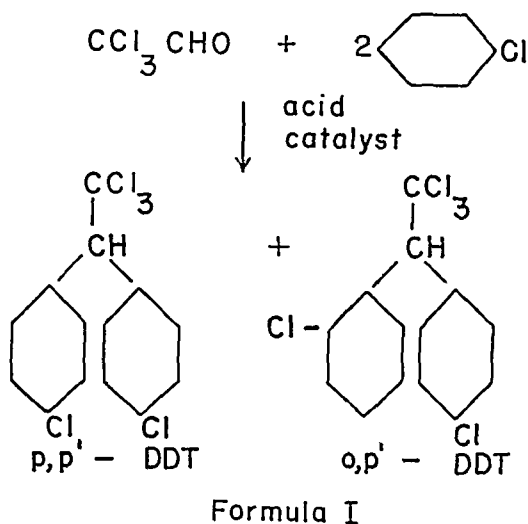
TABLE I.
FORMULA AND CHLORINE CONTENT OF SOME
CHLORINATED HYDROCARBON INSECTICIDES

Product	Formula	% Chlorine
DDT	$C_{14}H_9Cl_5$	50.01
TDE	$C_{14}H_{11}Cl_4$	44.33
Methoxychlor	$C_8H_{11}O_2Cl_2$	30.77
Benzene hexachloride	$C_6H_6Cl_6$	73.15
Chlordane	$C_{18}H_{11}Cl_7$	69.22
Toxaphene (chlor- inated camphene)	$C_{15}H_{11}Cl_7$	68.54

hydrogen chloride but are relatively non-toxic to insects. The speed at which the hydrogen chloride is released from the compound is not a vital factor either because DDT yields it quite rapidly whereas the methoxy analog of DDT does not.¹ Our knowledge of the relationship between insecticidal action and chemical constitution is too limited to state that any one reaction will determine whether a compound possesses insecticidal properties.

DDT

The studies leading to the discovery of DDT as an insecticide are presented in detail by Luger, Martin and Muller.² The symbol DDT is a contraction for Dichloro-Diphenyl-Trichloroethane. However, the term DDT has been confined to the product obtained on condensation of chloral with chlorobenzene in the presence of sulfuric acid. The chemistry of DDT has been investigated more extensively than that of the other chlorinated hydrocarbons.³ Formula I illustrates the formation of DDT.



When pure chloral and pure chlorobenzene are used the reaction product consists essentially of two isomeric compounds, p,p'-DDT and the o,p'-DDT. Technical DDT contains approximately 3 to 4 parts of the former isomer to one part of the latter.

The toxicity of these two isomers to several insects is shown in Table II.

TABLE II.

COMPARATIVE TOXICITY OF p,p'-O,p'-DDT TO VARIOUS INSECTS*

Insect	p,p'-DDT Concen- tration	Kill %	o,p'-DDT Concen- tration	Kill %
	%		%	
Houseflies	1.0	70	5.0	1
Body lice	0.05	100	1.0	0
Mosquitoes†				
Adults	0.5	49	5.0	23
Larvae	0.0015	50	0.011	50
	(p.p.m.)		(p.p.m.)	

* These results were obtained at the Orlando, Fla., laboratory of the Bureau of Entomology and Plant Quarantine.

† *Anopheles quadrimaculatus* Say.

It will be noted that although the o,p'-DDT is practically non-toxic to the adult form of these insects it is a very effective compound against mosquito larvae. This specificity manifests itself with many of the synthetic organic compounds.

It is natural to inquire as to the effect of replacing one or more chlorine atoms in DDT in both the benzene rings and the ethane part of the molecule with other atoms or radicals. Such compounds have been synthesized but more work has been done with analogs in which the chlorine atoms of the benzene rings have been replaced than with compounds in which the chlorine atoms in the ethane molecule have been substituted.

The toxicity of some analogs of DDT to mosquito larvae is given in Table III.

It is of interest to note that the replacement of chlorine atoms in the benzene ring by the hydroxyl radical gives a product that is relatively non-toxic. Methylation of the free hydroxyl group produces a potent insecticide. The product obtained with the methyl radical in place of chlorine is effective but that with the tertiary butyl group is of little value as an insecticide. Similar results were obtained when these

TABLE III.

TOXICITY TO FOURTH-INSTAR LARVAE OF ANOPHELES QUADRI-MACULATUS OF DDT ANALOGS IN WHICH CHLORINE ATOMS IN BENZENE RINGS HAVE BEEN REPLACED WITH OTHER ATOMS OR RADICALS*

Substituents on Diphenyltrichloroethane P.P.M. after 48 Hr.	Doseage, %	Mortality
<i>p,p'</i> -di-Cl (DDT)	0.005	100
<i>p,p'</i> -di-Br	0.005	100
<i>p,p'</i> -di-F	0.01	85
<i>p,p'</i> -di-CH ₃ O	0.01	100
<i>p,p'</i> -di-OH	10	20
<i>p,p'</i> -di-H	0.1	25
<i>p,p'</i> -di-CH ₃	0.01	100
<i>p,p'</i> -di-tert-Butyl	10	20
<i>p,p'</i> -Cl, H	0.01	85

* Deonier, C. C., Jones, H. A., Haller, H. L., Hinchey, E., and Incho, H. H., *Soap and Sanitary Chemicals*, 1946, 22:118.

compounds were tested against a number of agricultural insect pests.^{4,5}

Although *p,p'*-DDT is effective against a wider range of injurious insects than most of the other synthetic organic insecticides so far tested, it is not a panacea for all ills due to insects. DDT has little or no effect on the boll weevil, the cotton leafworm, the cotton aphid, the Mexican bean beetle, red spiders, cattle grubs, adults of the Florida and California red scales, the sugar-cane borer, orchard mites, the parlitaria date scale, and the plum curculio. It is effective against some aphids but as a rule is less effective than nicotine. It has also registered failures for one reason or another against the tobacco hornworm, the cabbage seedpod weevil, the tomato russet mite, etc.

METHOXYCHLOR

Methoxychlor is the coined name adopted for the methoxy analog of DDT, 1,1,1-trichloro-2,2-bis(*p*-methoxyphenyl)ethane. The technical product is obtained on condensation of chloral and anisole.⁶ Methoxychlor is effective against numerous agricul-

tural insect pests, including the Mexican bean beetle, and has been reported⁷ to give a more rapid "knockdown" of flies than DDT.

TDE (DDD)

TDE also called DDD is the symbol for dichloro diphenyl dichloroethane, a tetrachloro diphenyl ethane. *p,p'*-TDE is 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethane. TDE is obtained on condensation of dichloroacetaldehyde and chlorobenzene.⁸ The *p,p'*-TDE is equal in toxicity to *p,p'*-DDT against mosquito larvae⁹ and closely parallels DDT in effectiveness against both household and agricultural insect pests.³

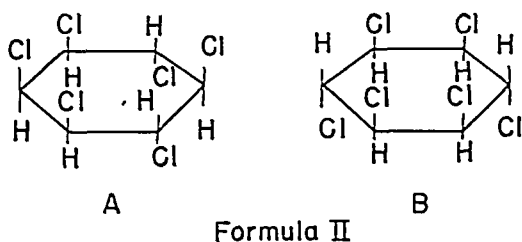
BENZENE HEXACHLORIDE

The insecticidal properties of benzene hexachloride or 1,2,3,4,5,6-hexachlorocyclohexane were discovered independently about the same time in France¹⁰ and England¹¹ during World War II while there was no communication between the two countries.

It is of interest that benzene hexachloride C₆H₆Cl₆ is insecticidal whereas hexachlorobenzene, C₆Cl₆, has no insecticidal properties.

Benzene hexachloride is prepared by the addition of chlorine to benzene in the presence of actinic light.¹² The reactants are required in the ratio of 3 moles of chlorine to one mole of benzene. It has not yet been possible to add chlorine to the three double bonds stepwise, that is, with the formation of dichloro or tetrachloro derivatives. When the ratio is other than three to one, the final product under all conditions so far tried, is a mixture of unchanged benzene and benzene hexachloride. The reaction product consists of a mixture from which five isomeric benzene hexachlorides have been isolated. These have been designated as alpha, beta, gamma, delta, and epsilon isomers. Their alphabetical designations indicate the order in which they have been discovered and described in the literature and bear no relation to their relative structures. Of these isomers only one, the gamma isomer, which occurs to the extent of 10-12 per cent in technical benzene hexachloride, has outstanding insecticidal properties.

The formation of the isomers may be explained in the following manner. If it is assumed that all of the carbon atoms of the cyclohexane ring lie in one plane eight stereoisomers of hexachlorocyclohexane, one of which exists in mirror-image form, are theoretically possible. The configuration shown in Formula IIa was originally assigned to the gamma isomer. This configuration has recently been shown to be incorrect and the isomer may be more nearly correctly represented by Formula IIb.¹³



Benzene hexachloride is toxic to a wide range of agricultural insect pests, especially the cotton boll weevil against which DDT is ineffective. The technical product has a musty persistent odor which may limit its usefulness for certain purposes.

Table IV shows the toxicity of each of four isomers to mosquito larvae. Like p,p'-DDT, the gamma isomer is slow in its killing action and does not cause "knockdown." At the time that these tests were made the epsilon isomer was not available.

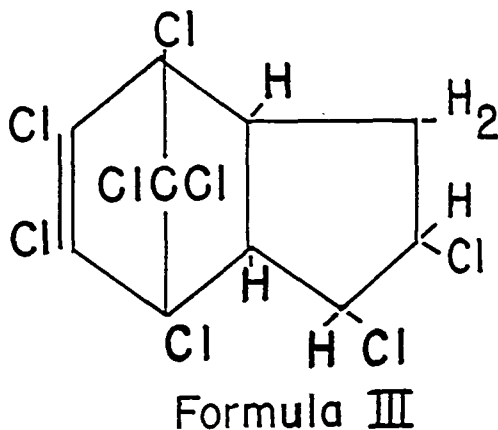
CHLORDANE

Chlordane is the common name assigned to the compound designated as 1,2,4,5,6,7,8,8-octachloro-4,7-methano-3a,4,7a-tetrahydroindan and having the structure shown in Formula III.

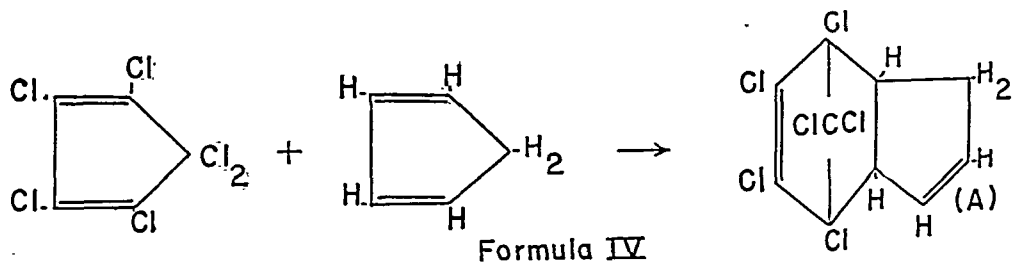
It is prepared by allowing hexachlorocyclopentadiene and cyclopentadiene to react as shown in Formula IV.

TABLE IV—TOXICITY OF VARIOUS ISOMERS OF BENZENE HEXACHLORIDE TO LARVAE OF ANOPHELES QUADRICIMACULATUS

Isomer	Dosage P.p.m.	Mortality in	
		24 Hours Percent	48 Hours Percent
Alpha	2.5	88	92
Beta	100	22	40
Gamma	.01	80	100
Delta	2.5	40	62
DDT	.01	98	100
	.005	53	85



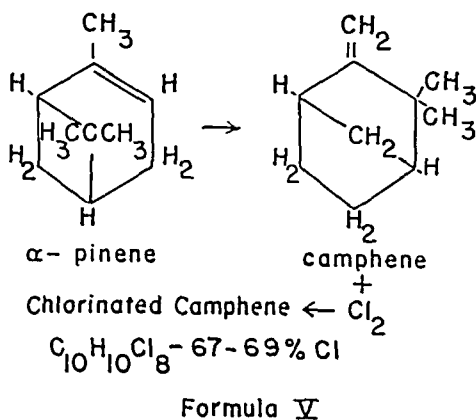
The adduct IV, dissolved in a suitable solvent, such as carbon tetrachloride, is treated with chlorine gas with the resultant addition of 2 atoms of chlorine to the double bond (A) to form chlordane (III).¹⁴ Technical chlordane contains 60-75 per cent of chlordane, the remainder being closely related compounds that occur in the normal process of manufacture and which are toxic to insects. Chlordane has been found to be toxic to a wide range of agricultural and



household insect pests.¹⁵ It is especially effective against grasshoppers and cockroaches and it has considerable residual effectiveness.

TOXAPHENE (CHLORINATED CAMPHENE)

Another chlorinated hydrocarbon with outstanding insecticidal properties is found among the terpene derivatives. The product was originally designated a chlorinated bicyclic terpene.¹⁶ Subsequently the coined name chlorinated camphene was developed for it. More recently this has been changed to toxaphene by which the technical product is now known. By the chlorination of camphene, which is obtained by the isomerization of pinene from pine wood extract, to a chlorine content of 67-69 per cent a product is obtained which has the approximate empirical formula $C_{10}H_{10}Cl_8$. The probable method of formation is given in Formula V although the exact structure is not known.

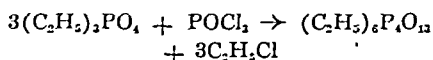


Toxaphene has been found toxic to a considerable number of agricultural insect pests, especially grasshoppers and insects attacking cattle.

ORGANIC PHOSPHORUS COMPOUNDS

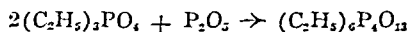
Three organic phosphorus-containing compounds, hexaethyl tetraphosphate, tetraethyl pyrophosphate, and parathion have received considerable attention for the control of injurious insects. Hexaethyl tetraphosphate is the name given by a German in-

vestigator to a product obtained by allowing triethyl orthophosphate to react with phosphorus oxychloride as shown in Formula VI.



Formula VI

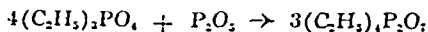
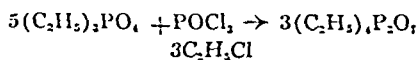
Essentially the same reaction product is obtained from triethyl orthophosphate and phosphorus pentoxide as indicated in Formula VII.



Formula VII

Chemical examination of hexaethyl tetraphosphate has shown it to be a mixture containing as its principal active ingredient the compound tetraethyl pyrophosphate. Other constituents are ethyl metaphosphate and triethyl orthophosphate, both of which are relatively insecticidally inactive materials. Pentaethyl triphosphate, an unstable ester possessing insecticidal properties, may also be present but this has not been established with certainty.

As produced by either of the reactions above tetraethyl pyrophosphate is present to the extent of about 15-20 per cent. Modification of either process by increasing the proportion of the triethyl orthophosphate results in a product of empirical formula $(C_2H_5)_6P_4O_{13}$, which is an even more potent insecticide than hexaethyl tetraphosphate. The reaction is shown in Formula VIII.



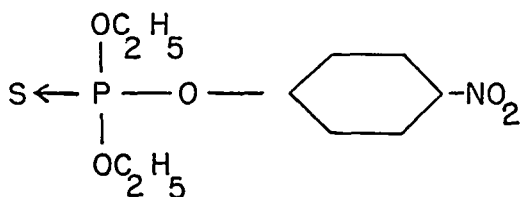
Formula VIII

The reaction products are not pure tetraethyl pyrophosphate but are mixtures of ethyl phosphates and polyphosphates containing approximately 40 per cent of this principal active ingredient.

German chemists had reported that in water solution or in the presence of atmospheric moisture hexaethyl tetraphosphate was completely hydrolyzed in 24 hours to ethyl alcohol and orthophosphoric acid. Hall and Jacobson¹⁷ in a study of the hydrolysis of hexaethyl tetraphosphate, however, found that although rapid hydrolysis to non-insecticidal products occurs, the end-products are monoethyl and diethyl orthophosphoric acid. Pure tetraethyl pyrophosphate hydrolyzes to diethyl orthophosphoric acid. This rapid hydrolysis to non-toxic products greatly limits the duration of the insecticidal effectiveness of tetraethyl pyrophosphate but it also eliminates the danger of toxic residues on the crops treated.

Both hexaethyl tetraphosphate and tetraethyl pyrophosphate are especially useful against mites and such soft-bodied insect pests as aphids, mealy bugs, and thrips. Both compounds have been shown to inhibit the action of cholinesterase¹⁸ and acetyl esterase.¹⁹

Another phosphorus-containing organic insecticide is O,O-diethyl O-p-nitro-phenyl thiophosphate Formula IX to which the coined name parathion has been assigned.



Formula IX

This insecticide also was discovered in Germany during World War II where it was designated E-605.^{20, 21}

According to Thurston²¹ the product is obtained by the following sequence of reactions: "Phosphorus trichloride is combined with sulfur by heating at 130°C. for two hours in a lead-lined autoclave. A quantitative yield of phosphorus thiotrichloride is obtained. The soluble sulfur compounds are removed by distilling the product from a lead-lined kettle. The resulting product boils at 125°/760 mm. pressure. This material is then combined with sodium ethox-

ide contained as a 10 per cent solution in alcohol. The formed diethoxythio-phosphorous chloride is poured into water and decanted. This intermediate product is stable in water and alcohol and only slowly decomposes when heated with them at temperatures of 80-90°C. Sodium p-nitrophenate in chlorobenzene is then combined with the diethoxy-thiophosphorous chloride by heating at 130°C. The finished product is not distilled, only the chlorobenzene, which is used as the reaction medium, is removed. The yield of the crude product is 80-90 per cent, since the formation of phosphorous thiotrichloride is quantitative (sic) and the remainder of the reactions are very good."

Parathion is an oily liquid with a disagreeable garlicky odor. It has a low vapor pressure of 0.0006 mm. of mercury at 24° and can be distilled only under greatly reduced pressure. It is not hydrolyzed appreciably in neutral water but is hydrolyzed in alkaline waters. It has proved highly toxic to all of a wide range of insects against which it has been tested. Since it is relatively stable, its effectiveness persists for a considerable time, reportedly from a few days to several weeks.

Both tetraethyl pyrophosphate and parathion are highly toxic to warm-blooded animals.²² They are absorbed through the skin and extreme care must be taken in using them. Moreover, in the case of parathion because of its greater stability there is the possibility of toxic residues from its application.

SUMMARY

Although much progress has been made in the development of new materials for combating insect pests many problems must be solved before their utility as practical control measures is determined. It is necessary to know against what kinds of insects the product is effective, the stage at which the insect is most susceptible—egg, larva, or adult—and the compatibility of the material with solvents, carriers, fungicides, or other insecticides. It must also be determined whether the material can be applied best as a dust, a spray or an aerosol and whether it causes plant injury when applied either to the foliage or to the soil. Its effect on

beneficial insects, such as bees and various parasites and predators, and its toxicity to warm-blooded animals, especially man, must also be ascertained. These and many other factors need to be established before a new product finds full use in the field of economic entomology.

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The Major Toxic Actions of Insecticides

ARNOLD J. LEHMAN

This review is an attempt to summarize the more important toxicological features of the commonly used insecticides. It should be stated at the outset that thousands of formulations involving probably not more than 25 insecticides are in existence. The solvents, diluents, and wetting agents which compose these formulations have some bearing on the toxic phenomena exhibited by the insecticides. In a good many instances these "inert ingredients" may be solely responsible for the injuries and it is not always possible to state definitely which of the ingredients should be incriminated. In the interest of accuracy, and to eliminate the side effects of the "inert ingredients," the toxic manifestations as given below for experimental animals were observed following the oral administration of poisons of high purity, either as such or in an innocuous solvent. It is impossible to state the fatal dose in humans for many of these insecticides and such doses can only be estimated from animal experimentation.

INSECTICIDES FROM VEGETABLE SOURCES DERRIS

The insecticidal quality of this plant is due to a number of constituents but principally rotenone.

Local effects. Rotenone, when applied to the skin, produces only an occasional mild irritation which persists about 24 hours after removal of the causative agent. Irritation of the conjunctiva may result on contact but no permanent damage has been reported. Rotenone is not absorbed by the skin.

Symptoms. The most pronounced effect of rotenone is upon respiration which is first stimulated and then depressed. If a sublethal dose has been ingested, stupor may be evident, and frequent convulsive seizures may be observed. Death is invariably the result of respiratory failure since the heart and blood pressure may be maintained for some time after cessation of respiration. The cardiovascular system is not seriously

affected even after massive doses of derris or its constituents.

Fatal dose. This is probably quite large, although guinea pigs do not survive after 60 mg./kg. dose administered orally. Dogs have tolerated as much as 2.0 gm./kg. It has been shown experimentally that finely powdered rotenone is about six times as poisonous as coarse crystals. Further, the intravenous toxicity of rotenone is 3,000 to 8,000 times the oral toxicity. When it is called to mind that the inhalation of finely divided substances produces effects of about the same order as those observed following intravenous administration, it can be seen that the inhalation of finely powdered rotenone or derris can become a very serious matter.

Fatal period. The onset of symptoms of poisoning may appear within a few minutes to a few hours, depending on the dose. Death can occur as early as 4 hours after ingestion of the poison or may be delayed for as long as 10 days with the crucial period falling between the first and second day.

Pathology. Pathological changes are almost always the result of chronic ingestion. A definite necrosis of cells in the central and midlobular areas of the liver has been a constant observation in chronically poisoned animals. Concentrations of derris root in the neighborhood of 75 parts per million in the diet have been reported as having produced these changes. This represents about 3.75 parts per million of rotenone. It has been estimated that the upper limit of tolerance for man is about 5 parts per million of derris in a diet consisting wholly of derris-contaminated food.

Treatment. Since rotenone acts as a gastric irritant and also stimulates the emetic center after absorption, these two factors operate to remove the swallowed material before serious poisoning occurs. No specific antidotes are known and treatment must be symptomatic.

PYRETHRUM

The active constituents are called pyrethrins. The pure substances are rare and the highest concentrations which may be encountered in commerce are 20 per cent pyrethrum extracts in soy bean or sesame oil.

Local effects. The pyrethrins are slightly sternutatory and possess an acrid bitter taste which is followed by a numbness of the tongue and lips. Highly concentrated extracts have been applied to human skin without signs or symptoms of irritation.

Symptoms. The pyrethrins produce a hyperexcitability. Incoordination, tremors, and muscular paralysis have been noted with death due to respiratory paralysis.

Fatal dose and period. The single acute oral dose is quite large in animals, being of the order of 1.5 gm./kg. Poisoned animals may die within 10 hours or may live 3 to 5 days or longer before succumbing.

Pathology. The toxicity of the pyrethrins appears to be so slight in warm-blooded animals that no tissue damage has been reported as caused by these agents. Allergic reactions and contact dermatitis have been reported in humans.

Treatment. Since household preparations contain the equivalent of about 108 mg. of pyrethrins per 100 cc. of kerosene, any toxic effects following the inadvertent swallowing of this solution would be due to the ingested kerosene. Gastric lavage is about all that can be recommended.

NICOTINE

This is one of the very few volatile, liquid alkaloids. It unites with acid to form water-soluble salts, the form in which it appears on the market.

Local effects. Tobacco and nicotine are strong local irritants. Nicotine penetrates the skin readily but its salts do not; hence strong solutions of the latter may be spilled on the skin without serious consequences.

Symptoms. Nicotine is one of the most rapid and deadly poisons known to man. The initial hot, burning sensation in the mouth, esophagus and stomach is followed by salivation, nausea and vomiting. Convulsion appears later which may be clonic and tonic in nature. Death is due to a curare-like paralysis of the respiratory muscles.

Fatal dose and period. About 60 mg. as a single dose appears to be the smallest quantity which can be fatal to man. It has been estimated that a 70-kilo individual can ingest a total of 280 mg. of nicotine daily in the form of tobacco without harm. The effects of chronic poisoning are those of inanition.

Treatment. There is no specific antidote for nicotine. Stomach lavage with tannic acid (strong tea or coffee), administration of charcoal or permanganate are aids in removing and destroying the poison. Artificial respiration is one of the most important life-saving measures and should be instituted as soon as respiratory collapse is apparent.

SYNTHETIC INSECTICIDES

LETHANES

These constitute a group of insecticides based on aliphatic thiocyanates, four of which have attained commercial importance.

Local effects. The local effects of solutions of the lethanes are due primarily to the vehicle (refined kerosene) in which they are dissolved. The concentrations of 2 or 3 per cent of active ingredient as ordinarily used are not high enough to cause skin irritation.

Symptoms. The symptoms are a deep depression, cyanosis, dyspnea, and tonic convulsions. Death is due to respiratory failure.

Fatal dose. Since the highest concentrations of the individual lethanes which may be encountered are 50 per cent solutions in kerosene, the additive effect of this solvent must be taken into account. A rough estimate would be 0.4 to 2 cc./kg. of the concentrates, with lethane-384 represented by the lower figure and thanite by the higher figure. Lethane-60 and lethane-384 special fall between these two extremes.

Fatal period. Fatal doses of the thiocyanates produce a rapid collapse and death within a few minutes. Occasionally, toxic effects are delayed for as long as 12 hours.

Pathology. No characteristic changes in tissues have been noted. The severe circulatory disturbances which the thiocyanates produce cause a marked hyperemia of the internal organs, hemorrhages, and edema. Degenerative changes in the brain, liver and kidney have been reported in chronically

poisoned animals.

Treatment. There is no specific treatment for poisoning by the thiocyanates. Removal of the poison from the gastrointestinal tract by the usual methods and treatment of symptoms as they arise are advised. Poisoning by these agents is an "all or none" phenomenon. If an individual survives the acute effects, recovery is practically assured.

DDT AND ITS ANALOGS

There are three members in this group, namely, DDT, methoxychlor, and TDE.

DDT

Local action. DDT is quite innocuous when applied to the skin. Solutions of DDT, however, are absorbed and multiple exposures do constitute a hazard. It has been estimated that daily exposures to solutions representing 9 grams of DDT, by spilling on the skin or clothing, may represent a quantity dangerous to man.

Symptoms. The symptoms of poisoning in mammals usually begin as tremors of the muscles of the head and neck. The tremors progress caudally and increase in intensity with time so that eventually purposeful movements are difficult or cannot be accomplished. Frequent episodes of tonic and clonic convulsive seizures manifest themselves. These convulsive seizures occur with increasing frequency, becoming almost continuous. A stage of depression is eventually reached, terminating in respiratory failure and death. An uncomplicated case of poisoning in man has not been reported, but from the meager information available it appears that giddiness, nervous tension and involuntary muscular tremors are some of the symptoms.

Fatal period. The onset of poisoning symptoms after oral ingestion of DDT may be delayed for several hours but can appear in one hour. The convulsive seizures are manifest within 30 or 40 minutes after the onset of tremors and death may occur 2 to 24 hours after the onset of the initial tremors.

Fatal dose. The fatal dose of DDT for man is not known. One report of a fatal case of poisoning estimates the dose as 500 mg./kg., representing about an ounce total

dose of the solid material.

Pathology. The gross pathological changes induced by DDT are not significant except in chronically poisoned animals. The outstanding lesions are found in the liver. Lighter grades of poisoning reveal a moderate degree of centrolobular hypertrophy of the hepatic cells, progressing to a combination of central necrosis and reparative hypertrophy in some cases of more severe intoxication. Some cerebellar changes of a degenerative nature have been observed in dogs. There is also a tendency to hepatic cell tumor formation in animals on long-term chronic ingestion of DDT.

Treatment. Treatment of acute poisoning should be directed toward removal of the DDT from the stomach and intestinal tract. Oil cathartics must be avoided. The chemical stability of DDT precludes the use of chemical antidotes. The neurological manifestations may be treated with an anticonvulsant drug, the best physiological antidote being phenobarbital. Enough should be given to control the tremors and convulsions. Experiments indicate that this dose is well below the anesthetic dose. DDT produces an excess excitability of the cardiac muscle so that any coincident sympathetic stimulation which accompanies the emotional disturbance induced by DDT convulsions can result in ventricular fibrillation. This can also be induced by a challenge dose of epinephrine which is, therefore, contraindicated in the treatment regimen.

METHOXYCHLOR

Local effect. Methoxychlor is only slightly irritating when applied to the skin. Solutions of the compound are absorbed by the skin, and multiple exposure to oil solutions representing about 36 grams daily can be dangerous to man.

Symptoms. Symptoms from a single acute dose of methoxychlor may not appear, since the quantities which must be ingested to produce toxic effects are so large it is rather doubtful whether an individual would swallow enough to cause poisoning. When symptoms do appear they are largely limited to a depression, although tremors have been noted in chronically poisoned animals.

Fatal dose and period. The fatal dose for

man is estimated to be in the neighborhood of 450 grams (1 pound) if ingested at one time. Onset of symptoms begins in about 24 hours but may not be evident for 72 hours. Death when it does occur is between 2 and 4 days after ingestion of the poison.

Pathology. Pathologic changes are seen only after subacute feedings of the poison at high levels in the diet (5000 parts per million) and are predominantly centered in the kidney. The damage consists of glomerular and tubular atrophy scattered diffusely throughout the organ.

Treatment. Probably little harm will be done if the material is swallowed. Removal of the insecticide from the stomach and intestinal tract is about all that should be necessary. Oil cathartics should be avoided.

TDE

Local effect. It is slightly irritating to the skin. Multiple exposures to oil solutions and the daily contact with quantities of about 6 grams total may be considered as the upper limit of tolerance for man.

Symptoms. The symptoms of TDE poisoning fall into the category of lethargy. Careful observations have not revealed convulsions, although these can be elicited by administering the poison intravenously.

Fatal dose and period. The fatal dose of TDE is about 10 times larger than that of DDT, which would place the total quantity at about 8-10 ounces of the solid material. The first symptoms of poisoning occur within 24 hours, with death within 48-96 hours after ingestion. Animals which survive after the 96th hour usually recover completely.

Pathology. TDE shows a predilection for the adrenal cortex, which may be briefly described as a marked chronic atrophy of the cortex. As with all chlorinated hydrocarbons, the liver shows damage similar to that described under DDT.

Treatment. This is the same as that given under methoxychlor.

OTHER CHLORINATED HYDROCARBONS

CHLORDANE

This insecticide is composed of several isomers and the true evaluation of its toxicology can only be made after each of the isomers has been subjected to study. The

comments below deal with the commercial products.

Local effects. Chlordane is moderately irritating to the skin. This property is lost on dilution, as in insecticide formulations, and the warning sign of danger is lost. The insecticide is absorbed through the skin, and it has been estimated that daily exposure to about 2.4 grams in solution may be dangerous to man.

Symptoms. The early signs are those of irritability of the central nervous system. This leads eventually into convulsions, which are followed by a period of depression. The process may be repeated several times, and death follows a terminal deep depression with or without a final convulsive seizure.

Fatal dose. From the acute standpoint chlordane appears to be only about one-half as poisonous as DDT, but the side effects are such that in the final analysis the toxicity is about 5 times that of DDT. Therefore, the fatal dose lies somewhere between 6 and 60 grams.

Fatal period. The onset of symptoms is within 45 minutes after ingestion. Deaths occur occasionally within 24 hours, are frequent between the 48th and 96th hour, and if survival extends to the 6th day, recovery is the rule.

Pathology. Inanition is a predominant observation in chronic poisoning, indicating a considerable disturbance in normal physiology. Of the vital organs, the liver bears the brunt of the poisoning, and the usual degenerative changes produced by chlorinated hydrocarbons are a constant finding.

Treatment. The usual measures should be adopted for removing the poison from the stomach and intestinal tract. Any additional treatment must be symptomatic as no specific antidotes are known.

BENZENE HEXACHLORIDE

The commercial product contains at least 4 isomers, each contributing to or modifying the effects of one on the other when administered in combination.

Local effects. The technical grades of benzene hexachloride (containing the 4 isomers, alpha, beta, gamma, and delta in varying proportions) are skin irritants, the damage being almost in direct proportion to the

amount of gamma isomer these mixtures contain. Toxic effects can be elicited by dermal application, and again the gamma isomer plays the leading role. The toxicity of this isomer increases 200 fold on repeated exposure, and dangerous quantities to man are probably of the order of a little more than 1 gram if repeated daily.

Symptoms. Animals which are poisoned with technical benzene hexachloride exhibit convulsions in some instances. This is followed by a hyperirritability to any outside stimulus (sudden noise, tapping the cage, etc.) and finally depression. When the symptoms of poisoning by the individual isomers are considered, the following facts are known.

Alpha induces a state of hyperexcitability which may develop into convulsions by any sudden stimulus.

Beta does not produce symptoms of poisoning from a single acute dose. If administered chronically, only tremors predominate at first but finally depression occurs and not unlike that observed with phenobarbital.

Gamma is a central nervous stimulant, the principal symptom being convulsions.

Delta acts as a depressant to the central nervous system.

Fatal quantity. Because the delta isomer is almost purely depressant in its effects, this component of the technical mixture has a tendency to antidote the stimulant actions of the other three components. This gives a rather wide range of dosage which may be fatal. Probably the best estimate for man would be 400 mg./kg. or about one ounce of technical benzene hexachloride containing 15 per cent gamma. Of the four isomers, Gamma may be met with frequently. The fatal dose is about one-half that of DDT and for man the fatal dose could be about 15 grams (one-half ounce) of the pure material.

Fatal period. The symptoms of technical benzene hexachloride poisoning begin within 1-2 hours after oral administration. The course of the fatal poisoning is not very rapid and death may be delayed for as long as 5 days. Gamma isomer is much more rapid in its action, the onset of symptoms developing within 30 minutes and death oc-

curing within 24 hours, and rarely delayed beyond this time period. Since 50-70 per cent of the technical benzene hexachloride is composed of the alpha isomer, it may be worthwhile mentioning that symptoms of poisoning of this isomer begin in about 24 to 48 hours and death may be delayed for 4 or more days.

Pathology. In a general way, benzene hexachloride isomers gave a pathological picture resembling that caused by DDT. Liver damage is the characteristic finding. Alpha and gamma isomers cause a moderate degree of hyaline granular degeneration of the renal convoluted tubular epithelium.

Treatment. There are no specific antidotes for benzene hexachloride, and treatment should follow the general plans given under DDT.

TOXAPHENE

This is a chlorinated derivative of camphene.

Local action. Toxaphene is moderately irritating to the skin. Absorption through the skin has been observed experimentally and the quantity which may be dangerous to man by daily contact has been estimated at 2.4 grams.

Symptoms. Toxaphene, being a derivative of a camphor-like substance, elicits responses quite similar to camphor. Epileptiform convulsions are a prominent feature.

Fatal dose. Toxaphene is about 4 times as toxic as DDT. The fatal dose for man may be estimated to be about 2-7 grams or a maximum of one-fourth ounce.

Fatal period. In poisoned animals toxic symptoms appear within an hour, with death following usually within 4 hours, or may be delayed for 24 hours.

Pathology. The major pathologic damage is located in the liver and does not differ much from the changes given under DDT.

Treatment. Evacuation of the stomach and bowels is indicated. Experimentally, the convulsions can be controlled by phenobarbital. Bromides are useful in controlling camphor convulsions and this probably also applies to toxaphene.

ORGANIC PHOSPHATES

There are two important members in this group, namely, tetraethyl pyrophosphate and

parathion. The toxic manifestations of these compounds are similar, but the mechanism of their poisonous action is considerably different from that described above for the other insecticides.

Local action. The organic phosphates are only slightly irritating to the skin. Both compounds penetrate the skin readily in all types of formulations. As little as 0.3 gram daily exposure has been estimated as dangerous to man.

Symptoms. The toxic manifestations of these two compounds are similar, the mechanism of their poisonous action being that of a cholinesterase inhibitor. The organic phosphates affect the postganglionic cholinergic nerves, that is, the nerves supplying smooth muscles and glands. This action has been termed the muscarinic effect. This action would manifest itself in man as follows:

- a. Lacrimation.
- b. Salivation.
- c. Sweating.
- d. Symptoms referable to the gastrointestinal tract, i.e., nausea, vomiting, diarrhea.
- e. Respiratory distress as the result of bronchiolar constriction. These symptoms may be exaggerated in individuals with asthmatic tendencies.
- f. Miosis and disturbance of vision.

The organic phosphates affect also the preganglionic and somatic motor nerves. This phase of their action is termed the nicotinic effect. The symptoms this action could produce may be listed as follows:

- a. Flushing of the skin.
- b. Throbbing in the head.
- c. Effects on the blood pressure.
- d. Various grades of heart block.
- e. Muscular tremors of peripheral origin.

To what extent convulsions enter the picture is problematical. All evidence points to the conclusion that the cerebral motor cortex is not involved. Convulsions, if they should occur, may be of asphyxial origin and not as the result of a direct action of the organic phosphates.

Fatal dose. The organic phosphates are from 3 to 5 times as toxic as nicotine. Since the fatal dose for nicotine is estimated as 60 milligrams (1 grain), 12 to 20 milligrams ($1/5$ to $1/3$ grain) of parathion or tetraethyl pyrophosphate may be considered as a poisonous quantity and liable to prove fatal.

As little as 0.05 cc. (1 small drop) of the concentrated materials splashed into the eye may be fatal.

Fatal period. Onset of symptoms and time of death depend somewhat on the quantity ingested. In a general way, toxic effects make their appearance within 30 minutes, and death in the majority of fatal poisonings occurs between $1\frac{1}{2}$ and 4 hours.

Pathology. In acute poisonings little of note is observed. In chronically poisoned animals enterocolitis and necrosis of the gall bladder are the predominant injuries.

Treatment. The usual measures for removal of the poison from the stomach and intestinal tract are recommended. Atropine sulfate is a physiological antidote for the muscarinic effect of the organic phosphates. Most of the first group of symptoms listed above would be alleviated by a 0.5 to 1.0 mg. dose. Whether or not this dose should be repeated would depend on the response of the patient. The development of mydriasis and dry mouth and throat is an indication that enough atropine has been given, and nothing could be gained by administering more of the drug.

Atropine does not antidote the nicotinic action of the organic phosphates. Peripheral muscular depressants appear to be of some value for controlling the tremors. Curare has this effect, but the therapeutic margin is quite narrow. The parenteral administration of magnesium sulfate may be a better choice. When magnesium is given parenterally one must guard against respiratory failure. Calcium successfully counteracts this action and it is therefore advisable that a solution of calcium chloride or gluconate for intravenous administration be available should the magnesium dosage be exceeded.

INSECTICIDE ACTIVATORS

This includes a group of compounds which will enhance the insecticidal effect of derris and pyrethrum. Two compounds, N-propyl isome and piperonyl butoxide, are of commercial importance at present.

These compounds are relatively inactive pharmacologically. The quantities necessary to produce poisoning are quite large, being of the order of 10-12 grams per kg., so that the hazards from ingesting a single dose of these materials appear to be of minor importance.

*Recent Advances in Medical and Veterinary Entomology*¹

E. F. KNIPLING

Arthropods which attack man and animals affect directly or indirectly the lives of every individual in the world. The hundreds of species involved include vectors of important diseases such as malaria, typhus, bubonic plague, yellow fever, and many others, which have plagued mankind with devastating epidemics during the past. Many factors must be considered when methods are being developed for the control of arthropods attacking man and animals. However we could, until recently, hardly look with pride on the progress that had been made in overcoming some of the major obstacles to improved health standards and world economy. It is not generally known, for example, that during and after World War I there were more casualties in Europe due to louse-borne typhus than were caused by the World conflict. Furthermore, at the beginning of World War II we were little better prepared to control lice or typhus epidemics than during World War I.

Fortunately progress during the last 7 or 8 years in controlling arthropods which attack man and animals has been phenomenal. No field of biological science has shown greater progress during the same period of time. It is possible today to break, within a few days or weeks, epidemics of human diseases such as louse-borne typhus, malaria, dengue, sand fly fevers, and a number of other important diseases. Important progress also has been made in the veterinary field of insect control.

The great progress in the field of medical and veterinary entomology can be attributed largely to the discovery and development of a number of highly effective insecticides and repellents as well as methods and equipment

for their application. The most important of the new chemical agents for controlling arthropods is the well-known insecticide DDT.

However, the true value of DDT in the future might not be the continued use of this insecticide for controlling arthropods but rather that it has pointed the way for achieving insect control with a degree of efficiency hardly considered possible as late as 10 years ago. There are in fact several new insecticides available today, and others in the early stages of investigation, which in some respects are superior to DDT. Among the newer promising chemicals available for controlling arthropods affecting man and animals are benzene hexachloride, chlordane, toxaphene (chlorinated camphene), methoxychlor, TDE (also called DDD), several synergists for pyrethrum, and various insect repellents.

Along with the development of the highly effective insecticides and their widespread use for the control of insects affecting man and livestock, it should be pointed out that new problems have arisen, the chief one being the question of toxic effects of these materials to man, animals, and wildlife. There is no evidence at present that the widespread use of DDT has caused harmful effects to man and animals. Available toxicological data and the absence of serious toxic reactions resulting from its use suggest that this material, as well as some of the related insecticides, is not likely to result in acute toxicity hazards if employed with reasonable precautions. Likewise, there is no evidence of serious upset of nature's balance of beneficial forms of animal life when DDT is applied over large areas for controlling insects such as mosquitoes.

Although toxicity studies with some of the new chemicals have been pursued rather extensively, toxicologists are concerned about the possible long-range accumulative effects of some of these materials when man or animals are repeatedly exposed to them or

¹Most of this review deals with first-hand information made available to the writer by several laboratories of the Bureau of Entomology and Plant Quarantine, principally those located at Orlando, Florida, and at Kerrville, Texas. The investigations at Orlando were supported by grants from the Office of Scientific Research and Development during 1942-45, and since that time funds for the research were made available by the National Military Establishment.

when they are consumed in small quantities over a period of years. Most of the new insecticides have gone into use in the medical and veterinary fields without adequate knowledge regarding their acute or chronic toxicity hazards. There is probably no problem in the medical and veterinary entomological fields more urgent than intensified research to study all aspects of the toxicity of known and newly developed insecticides and insect repellents. On the basis of comparative toxicity, most of the newer materials are of a lower order of toxicity than are the arsenicals and some of the other old insecticides which have been employed for many years. However, more extensive use of the new insecticides under almost every conceivable condition permits greater and more varied opportunity for man and animals to become exposed.

The purpose of this paper is to summarize in a general way the recent advances in the control of insects, ticks, and mites which attack man and animals. There have been so many new developments that the writer has not found time to present detailed information regarding them, nor has he found it practical to give credit to the many individual investigators who have been responsible for the rapid progress.

RECENT ADVANCES IN MEDICAL ENTOMOLOGY

Three methods are generally employed in controlling arthropods attacking man. In a broad sense these methods might be classified as follows: 1) Personal protective measures, 2) premise treatments, and 3) area control measures. All three methods might have to be applied to obtain maximum protection, but this depends on the type of arthropod involved and the circumstances existing in a given area.

PERSONAL PROTECTIVE MEASURES

Recent investigations on the measures to use for personal protection have been principally along two lines—1) research on insect repellents for use on the skin to protect individuals from attack by mosquitoes, black flies, sand flies, and other similar insects, and 2) the development of repellents or toxicants largely for treatment of cloth-

ing to protect individuals from attack by human lice, mites, ticks, fleas, and mosquitoes.

Mosquito repellents.—During the recent war, dimethyl phthalate, Indalone (*n*-butyl mesityl oxide oxalate), 2-ethyl hexanediol-1, 3, and a 60-20-20 mixture of these three materials in the order named were developed for the Armed Services as repellents for mosquitoes, black flies, sand flies, and other related insects. Several thousand compounds were tested during and since the war, and a number of other repellents have been developed which are of the same general order of effectiveness as those mentioned. Included among these are dimethyl carbate; *N*, *N*, diethylsuccinamic acid, *n*-propyl ester; and ethyl beta-phenyl-beta-hydroxy propionate. Repellents vary considerably in their degree of effectiveness, the results depending on the kind and species of insect and the conditions under which the repellents are employed. However, they will usually protect individuals from mosquitoes and black flies for periods of 1 to 4 hours. Considerable effort has been devoted to developing repellents for treatment of clothing to prevent mosquitoes from biting through. The repellents mentioned, especially Indalone, will provide considerable protection. A number of other materials as effective as or more so than Indalone are now being investigated.

Miticides.—Among the most annoying pests of man in the United States are the small mites (*Eutrombicula* spp.) commonly called chiggers or red bugs. However, in some parts of the world the chigger mites are of greater importance because they are vectors of a rickettsial disease, scrub typhus. Dimethyl phthalate, butyl phthalate, and benzyl benzoate were employed successfully during and immediately after the war by the Allied Armed Forces. Recently, however, several materials have been developed at the Orlando laboratory which are far more persistent than those mentioned. Among the most effective are benzil, diphenyl carbonate, and *p*-cresyl benzoate. These materials impregnated into clothing at the rate of about 2 ounces for the average army uniform will provide complete or nearly complete protection against chiggers

in Florida after the clothing has been laundered four to six times.

Louse and scabies control.—The successful use of DDT for controlling the body louse (*Pediculus humanus corporis* Deg.) during and since the war is well known. DDT at a concentration of 10 per cent was most generally employed. A DDT dust treatment will provide excellent control of body lice as well as head lice (*Pediculus humanus humanus* L.), and is the most practical method of applying the insecticide for this purpose. However, considerable research has been directed toward developing the impregnation method of employing DDT. When the treatment is used in this way, it is much more persistent. When ordinary woolen underwear is treated with solutions or emulsions containing 1.5 to 2 per cent of DDT, the garments will control lice even after they have been laundered four to six times. In case of a national emergency the treatment of underwear before it is issued to the servicemen in combat areas seems to offer possibilities of protecting them from lice during entire campaigns.

Aside from the use of dusts and impregnated garments, DDT has controlled human lice when used in a special liquid preparation known as the NBIN formula. This preparation in the concentrated form contains 68 per cent of benzyl benzoate, 6 per cent of DDT, 12 per cent of benzocaine, and 14 per cent of Tween 80 (an emulsifying agent). When diluted at the rate of 1 part of the concentrate in 5 parts of water and thoroughly applied, the treatment will provide complete control of head lice, body lice, or pubic lice (*Phthirus pubis* (L.)) on individuals. The benzyl benzoate was chosen as the principal solvent for the concentrate so that the formula could also be used for controlling the itch mite (*Sarcoptes scabiei* Deg.). A single thorough treatment with the diluted preparation will eliminate scabies infestations.

Some of the other new insecticides, such as toxaphene, chlordane, and benzene hexachloride, are also highly effective louse-killing agents. Toxaphene, in particular, is superior to DDT when used as a dust or when impregnated in clothing. Chlordane is

of about the same order of effectiveness as DDT, whereas benzene hexachloride is highly effective but less persistent than DDT. However, these materials are not recommended for louse control at the present time because of insufficient information relative to their toxicity to man.

Tick repellents and toxicants.—There is increasing interest in the development of treatments that will protect individuals from attack by ticks. These arthropods not only cause discomfort but they transmit several rickettsial and other diseases to man. Considerable progress in developing clothing treatments effective against ticks has been made during recent years. During the war, the results of research at the Orlando laboratory demonstrated that dimethyl phthalate, Indalone, and benzyl benzoate offered considerable protection when applied to clothing. Since the war a number of promising tick repellents or toxicants have been investigated by the Orlando laboratory and by the U. S. Public Health Service. Among the most promising new materials against the lone star tick (*Amblyomma americanum* (L.)) are N-(n-butyl) acetanilide; n-hexyl ester of mandelic acid; beta-phenyl-beta-hydroxypropionic acid, ethyl ester; and diethylphthalate.

Flea repellents and toxicants.—DDT powders will control fleas when applied to infested individuals. The insecticide kills the fleas rather slowly and therefore considerable effort has been devoted to the development of more desirable treatments for individual protection. Powders containing 10 per cent of DDT and 0.1 to 0.2 per cent of pyrethrins plus 0.5 to 1 per cent of piperonyl butoxide or N-isobutylundecylenamide are at present considered promising treatments. In addition to the development of dust treatments, efforts have been made at the Orlando laboratory to develop clothing treatments which will prevent flea infestations. A number of promising compounds under investigation include benzyl benzoate, phosphoric acid, tributyl ester, and caproic acid 1.5 pentanediol monoester.

PREMISE TREATMENT

The development of highly effective and long-lasting treatments for controlling in-

sects that invade homes and other buildings has, without doubt, represented the greatest single advance in the field of medical entomology. The value of DDT as a residual insecticide for controlling mosquitoes, flies, sand flies, fleas, bedbugs, and other insects is well known. For this reason the discussion of new insecticides will be largely restricted to a summary of the performance of new insecticides other than DDT. However, before proceeding with this summary the subject of insecticide-resistant arthropods will be discussed.

Insecticide-Resistant Arthropods.— Until very recently DDT was employed with phenomenal success in controlling the house fly (*Musca domestica* L.). However, during 1948 numerous reports from the United States and some from other parts of the world have indicated that this insect in certain localities is no longer being controlled with DDT residual sprays. Because of the importance of these failures, the Bureau of Entomology and Plant Quarantine, the New Jersey State Agricultural Experiment Station, the California Agricultural Experiment Station, the U. S. Public Health Service, and a number of commercial concerns dealing in insecticides, initiated intensive investigations to determine the cause. This problem has also been studied in Italy, Switzerland, and other nations. Most, if not all, of the institutions investigating the problem have come to the conclusion that house flies in some areas have developed a marked resistance to DDT.

The magnitude of this resistance can be illustrated by summarizing some of the research conducted at the Orlando laboratory. In 1945 studies were initiated to determine whether house flies were likely to develop DDT-resistant strains. When the flies were subjected to treatments with DDT space sprays, so that only about 5 to 10 per cent of each generation survived to perpetuate the colony, a strain two or three times as resistant to DDT as the parent strain was developed after about 15 generations. This special colony was not only more resistant when DDT was applied as a space spray but also when it was exposed to DDT residual treatments. As the selection continued through subsequent generations, the colony

became more and more resistant to DDT. To obtain equal kill of the nonresistant and resistant strains during the 55th to 60th generations, the concentration required for the resistant strains was over 100 times that required for the nonresistant strain. When measured from the standpoint of immunity to residual deposits, the exposure time for approximately 100 per cent kill of the resistant strain was 16 hours or longer (approximately 1,000 minutes) as compared with approximately 5 minutes for the flies from the parent nonresistant stock.

When reports of DDT failures were received during 1948, wild house flies were collected from several states around dairies where DDT has been used for 2 to 3 years. Tests with these flies have shown that certain strains require from 30 to 40 times the period of contact with DDT-treated surfaces to produce the same percentage mortality obtained with laboratory strains of house flies that have not been exposed to DDT.

It is doubtful whether anyone expected such magnitude of resistance to develop among house flies within 2 or 3 years. This problem is considered a highly significant adverse development in the medical entomology field. Reports of DDT-resistant bedbugs (*Cimex lectularius* (L.)) have also been received; however, carefully controlled research has not been conducted to confirm them. There are no indications of DDT-resistant strains of *Anopheles* mosquitoes, but there is no reason to doubt that such strains might develop among some of the hundreds of species which occur throughout the world.

The dramatic occurrence of insecticide-resistant house flies and the possibility that other species might develop such resistance should serve to emphasize the need for continued research in the field of medical and veterinary entomology, even though effective materials and methods of controlling various species might be currently available.

Performance of New Insecticides—Benzene hexachloride.—The insecticidal and acaricidal value of benzene hexachloride was discovered in France and Great Britain, but much of the research during recent years has been done in the United States.

The gamma isomer of benzene hexachloride is among the most active of the new insecticides against insects, ticks, and mites. However, its rather high degree of toxicity to higher animals and its musty odor are factors which tend to limit the widespread use of this material for controlling some of the species.

Against flies and mosquitoes gamma-benzene hexachloride employed as a space spray is considered more effective than DDT, but the residual action of this insecticide is generally less persistent than that of DDT. DDT-resistant strains of house flies, already discussed, show relatively little resistance to benzene hexachloride. Investigators at the California Agricultural Experiment Station at Riverside have reported satisfactory control of house flies for several weeks with benzene hexachloride in dairy barns where DDT has failed.

Chlordane.—Chlordane, discovered by the insecticide industry in the United States, is also effective against a wide variety of insects which invade homes. It has been widely used with outstanding success for the control of such insects as cockroaches and ants. When used as a space spray, chlordane is somewhat more effective than DDT against house flies, but is less so when employed against adult mosquitoes. Although residual treatments of chlordane are normally less persistent than DDT against house flies and mosquitoes, chlordane is more effective than DDT against DDT-resistant house flies. Chlordane is therefore a promising treatment for fly control. However, further study is necessary under a wide range of conditions and against various strains of house flies before its true value for this purpose can be determined.

Methoxychlor.—The methoxy analog of DDT, known as methoxychlor, approaches DDT in effectiveness when used as a space spray or a residual spray against house flies. However, it was given little consideration for practical application because it costs more and proved considerably less effective than DDT against mosquitoes and certain other insects of medical importance. Recently, however, it has shown considerable promise as a control for DDT-resistant house flies. In laboratory studies these flies

have shown considerably greater tolerance to methoxychlor than normal strains but not to the same extent as to DDT. The insecticide is suggested as a trial substitute under conditions where DDT has failed. However, as with chlordane, more study under various conditions is needed before the true value of methoxychlor in controlling house flies can be determined. When compared with DDT and other chlorinated hydrocarbons now available, methoxychlor is considered much less toxic to warm-blooded animals.

Piperonyl butoxide.—Piperonyl butoxide is the best known and most generally effective of an interesting group of compounds which increase the insecticidal activity of pyrethrum. When employed in proper proportions, piperonyl butoxide will increase the toxicity of pyrethrum to house flies approximately 10 times. It is therefore being used extensively in space sprays and aerosols.

Piperonyl butoxide also increases the activity and prolongs the action of pyrethrum, when the combination is used as a residual spray for certain insects which invade buildings. N-Propylisome is another new synergist for pyrethrum which is coming into widespread use.

AREA CONTROL MEASURES

The most spectacular advance in the field of medical entomology has been the development of DDT during the war for controlling mosquitoes, both adults and larvae, when applied in small amounts as sprays or aerosols. Although no outstanding new insecticides have been developed since then, there has been steady progress in the development of more efficient equipment for applying DDT from aircraft and of several new types of ground equipment for producing sprays and aerosols (fogs). DDT is now being used extensively in amounts ranging from 0.05 to 0.25 pound per acre for controlling adults and larvae of various species.

Perhaps the outstanding new advance in area control of arthropods has been the work on black flies (Simuliidae), mites, and ticks. Several new insecticides and acaricides have been investigated in connection with the control of these parasites.

Black Flies.—As a result of some early preliminary investigations in South and Central America by the Rockefeller Foundation, it was known that DDT offered considerable promise for the control of black fly larvae breeding in streams. Investigations of the various new insecticides for controlling black flies in North America were not initiated until about 1947. However, during 1947 and 1948 the United States Bureau of Entomology and Plant Quarantine, the National Military Establishment, and the Canadian Department of Entomology have conducted extensive investigations on the control of black flies. These studies have shown that black fly larvae can be controlled with minute amounts of DDT applied to infested streams.

In Alaska oil solutions of DDT applied from the air at the rate of 0.1 pound of DDT per acre to 800-foot sections of streams controlled black fly larvae for at least 2 to 3 miles down stream.

The Canadian workers have recently reported that black fly larvae breeding in large streams were controlled for a hundred miles or more when DDT was applied. The Bureau of Entomology and Plant Quarantine demonstrated that DDT applied for gypsy moth control completely eliminated black fly larvae in streams in an area of fifty thousand acres. Thus far DDT has not been employed in practical control operations. Studies are underway by the Fish and Wildlife Service, in cooperation with several agencies, to determine whether such control procedures will have any serious effects on fish. The minimum amount of DDT needed to control black fly larvae is far below the toxic level for fish, but further studies should be made to determine the effects of the treatment on aquatic insects and other fish foods.

Investigations in New Hampshire by the Orlando laboratory have shown that TDE is more effective than DDT for controlling black fly larvae. It is also less toxic than DDT to certain fish and may therefore be more useful than DDT for black fly control.

Considerable success in controlling black fly adults in the New England States by means of DDT aerosols has been achieved by workers of the New York State Agri-

cultural Experiment Station. However, the cooperating agencies mentioned in connection with the studies on black fly larvae failed to demonstrate satisfactory control of black fly adults in Alaska and Canada when DDT was applied as sprays or aerosols, because of rapid migration of the insects into treated areas from surrounding untreated areas.

Chiggers and Ticks.—Workers at the Orlando, Florida, and Savannah, Georgia, laboratories of the Bureau of Entomology and Plant Quarantine have shown that chigger mites (*Eutrombicula* spp.) can be effectively controlled in their natural habitats with dusts or sprays of some of the new insecticides. Benzene hexachloride, chlordane, and toxaphene applied at the rate of 2 pounds per acre will provide excellent control. These insecticides, as well as DDT, are also highly effective in controlling ticks, particularly the lone star tick. The New York Agricultural Experiment Station and the Bureau of Entomology and Plant Quarantine have also demonstrated effective control of the American dog tick (*Dermacentor variabilis* (Say)) with DDT applied at the rate of 1 pound per acre.

Mosquitoes.—A number of the newer insecticides have been investigated as mosquito larvicides and adulticides by agencies such as the U. S. Public Health Service, the Bureau of Entomology and Plant Quarantine, the Tennessee Valley Authority, and a number of State mosquito-abatement organizations. None of the compounds has proved as effective as DDT in controlling adult mosquitoes when applied under outdoor conditions. However, as a mosquito larvicide, TDE is equal to and in some cases superior to DDT.

Parathion is highly effective against mosquito larvae and adults. It is so highly toxic to warm-blooded animals, however, that it is questionable whether it can be used for mosquito control.

RECENT ADVANCES IN VETERINARY ENTOMOLOGY

Time and space will not permit a thorough review of recent research in the field of veterinary entomology. However, as in the field of medical entomology, great prog-

ress has been made. The advances have for the most part been due to the high degree of effectiveness of some of the new insecticides for controlling several important livestock pests. The most important of the new insecticides for controlling animal parasites is DDT. However, the performance of this insecticide in the livestock-pest field is well known, and it will be mentioned only as a standard of comparison in reviewing the results reported with the newer chemicals.

This discussion will touch only incidentally on the important toxicological problem. However, as in the field of medical entomology, the widespread use of some of the newer insecticides for controlling livestock insects has raised important questions relative to the hazards of their use, not only to the livestock but also to the consumers of animal products from treated animals. Following the discussion of the new insecticides, a brief review will be given of some recent and interesting work in the field of internal medication for controlling external animal parasites.

NEW INSECTICIDES FOR CONTROLLING LIVESTOCK INSECTS

Benzene hexachloride. Benzene hexachloride is effective in controlling a number of parasites of livestock. All the species of lice attacking livestock are highly susceptible to this insecticide. It is not only effective against the motile forms but it also possesses some ovicidal properties. A spray containing 0.25 to 0.5 per cent of technical benzene hexachloride (10-12 per cent of the gamma isomer), or 0.25 to 0.05 per cent of the gamma isomer, will provide satisfactory control of both *Anoplura* and *Mallophaga* on cattle. The technical grade is at least as effective and possibly more effective than DDT at the same concentrations. The insecticide is also highly effective against all stages of several species of ticks attacking livestock in this country. Concentrations as low as 0.25 per cent of the technical material (0.025 per cent gamma) will kill engorged forms of the lone star tick and the winter tick (*Dermacentor albipictus* (Pack.)). A concentration of 1.5 per cent or even higher percentages of DDT are required to kill engorged forms of these spe-

cies. However, benzene hexachloride has less persistence than DDT and some of the other new materials, and animals are subject to reinfestation within a short time after treatment.

Benzene hexachloride is also highly effective in controlling the sheep tick (*Melophagus ovinus* (L.)) and is superior to DDT. However, rotenone, which has been used extensively for the control of the sheep tick, is also highly effective and from the standpoint of economy and safety is perhaps the best all-round treatment for this parasite.

Benzene hexachloride, according to investigations by the Bureau of Animal Industry, various livestock associations, State experiment stations, and industrial concerns, is highly effective for controlling the mange mite and other mites on swine, cattle, and sheep.

The acute toxicity of benzene hexachloride to livestock is rather high, since it has been shown that young calves less than 3 months old may show toxic symptoms when thoroughly treated with sprays containing 0.05 per cent of the gamma isomer. However, yearlings or older cattle have shown no toxic reactions when treated repeatedly with concentrations of 0.15 per cent to 0.2 per cent of the gamma isomer. The musty odor of benzene hexachloride is also objectionable, and there has been some concern over possible tainting of flesh or milk of animals treated with this insecticide. However, there has been no clean-cut evidence that tainting has occurred when the insecticide has been employed in actual practice.

Chlordane.—Chlordane in general is comparable with DDT against various livestock pests, such as all species of lice attacking cattle, sheep, goats, and swine. It is distinctly more effective than DDT against the sheep tick. It is also more effective than DDT against engorged forms of the lone star tick and the winter tick. Concentrations of 0.5 to 0.75 per cent will destroy all stages, whereas 1.5 per cent or more of DDT is required to kill engorged adults. The protection against reinfestation offered by chlordane against the lone star tick is comparable with that of DDT, whereas against the winter tick chlordane is superior to DDT.

For control of the horn fly (*Siphona irritans* (L.)) chlordane is somewhat less effective than DDT, although good control can be obtained when it is applied in the amounts generally used for DDT.

Although chlordane has been used rather extensively in certain areas for controlling livestock pests, apparently without harmful effects, the insecticide is known to produce toxic effects when sprays containing 1.5 to 2 per cent are thoroughly applied at frequent intervals to cattle, sheep, and goats. For this reason further toxicological study employing minimum concentrations needed to control certain parasites should be conducted to determine whether the insecticide can be employed without harmful effects to the host.

Toxaphene.—Toxaphene in general is at least comparable with DDT and chlordane for controlling the various species of lice attacking farm animals. It is also one of the most promising of the new materials for the control of various ticks attacking livestock. For these parasites the insecticide appears to be at least equal to chlordane and generally superior to DDT.

For horn fly control toxaphene is somewhat slower in action but of the same general order of effectiveness as DDT. For sheep ticks it is more effective than DDT but less effective than chlordane or benzene hexachloride.

The reason for delay in recommending the use of toxaphene as a general-purpose insecticide for controlling insects and ticks attacking livestock is the lack of information regarding its toxic effects to animals. In practical control operations some cattle, principally calves, have died after being dipped in toxaphene dips containing 0.55 per cent of the insecticide. It has been fairly well established that the deaths occurred largely because the emulsion formulations had decomposed before they were used, and as a result the dip was improperly mixed. Controlled toxicological tests have shown that the sprays or dips containing from 1.0 to 1.5 per cent concentrations of toxaphene might prove toxic to young calves. However, cattle a year or more of age have been treated repeatedly with 1.5 to 2 per cent concentrations without apparent toxic

effects.

It is possible that toxaphene properly formulated and carefully mixed and applied can be used with safety on livestock. However, further studies on various aspects of the toxicology of this insecticide must be undertaken before its potential use for the control of livestock pests can be determined.

Piperonyl butoxide.—Piperonyl butoxide, discussed in connection with the control of certain insects affecting man, is also being employed in combination with pyrethrum for controlling certain livestock pests. This combination will provide satisfactory control of lice on cattle when applied at a concentration as low as 0.005 per cent of pyrethrins and 0.05 per cent of piperonyl butoxide. It also offers promise for the control of flies attacking livestock. The chief advantage offered by pyrethrum is its low toxicity to higher animals. According to investigations by the Food and Drug Administration, piperonyl butoxide is also of a very low order of toxicity to higher animals.

Methoxychlor.—Methoxychlor is the least toxic to higher animals of the various new chlorinated hydrocarbon insecticides. It is an effective insecticide for controlling horn flies and lice on cattle and is only slightly less effective than DDT against the former and about equal to DDT against the latter. The widespread use of DDT on dairy cattle and the appearance of small amounts of this insecticide in the milk following its use is creating some concern among toxicologists. No significant amounts of methoxychlor have been demonstrated in milk of dairy animals following its use as a 0.5 per cent spray. This observation, together with its inherent lower toxicity, makes methoxychlor of special interest for controlling insects affecting dairy animals. The material is somewhat more costly than DDT or some of the other insecticides.

TDE.—TDE is of about the same order of effectiveness as methoxychlor against horn flies and lice on cattle. According to the Food and Drug Administration, the degree of toxicity of TDE to warm-blooded animals is intermediate between that of DDT and methoxychlor. Investigations by the Bureau of Entomology and Plant Quarantine have shown that the amount of in-

secticide appearing in the milk of dairy animals treated for horn fly control is somewhat less than the amount following the use of DDT. The average for DDT during a season's schedule of spray-treatment for horn fly was about 0.6 to 0.7 part per million, whereas the average for TDE was about 0.4 part per million.

CHEMOTHERAPEUTIC AGENTS FOR CONTROLLING
ARTHROPOD PARASITES OF ANIMALS

The possibility of controlling arthropod parasites of animals following the feeding or injection of chemicals has been considered by entomologists and parasitologists for many years. Until recently no material was known which would control any of the parasites attacking animals. However, during the last few years several investigators have demonstrated that certain blood-sucking external parasites can be destroyed by administering chemicals to the host. Investigators at the Orlando laboratory first demonstrated that bedbugs were killed when they were permitted to take blood from rabbits given large doses of DDT or pyrethrum. Subsequent research demonstrated that human body lice, which fed on rabbits, were killed when 2-pivalyl-1,3-indandione in single doses as low as 2.5 mg. per kilogram of body weight was ad-

ministered orally or injected into the host. Although these doses might have caused toxic reactions, no gross symptoms of toxicity were noted. This same material has controlled sucking lice on swine and dogs when administered at the rate of 5 to 10 mg. per kilogram of body weight (unpublished data obtained by the Kerrville, Texas, and Corvallis, Oregon, laboratories of the Bureau of Entomology and Plant Quarantine).

British investigators have shown that bedbugs (*Cimex* spp.), yellow-fever mosquitoes (*Aedes aegypti* (L.)), and certain ticks were killed when fed on rabbits given benzene hexachloride. Other investigators in Hungary have recently reported controlling mites and lice on animals by oral administration of chemicals to the host.

Investigations in the field of chemotherapy have by no means progressed to a stage where chemical agents can be administered internally for the control of external parasites. Chemicals such as benzene hexachloride and 2-pivalyl-1,3-indandione are quite toxic to animals. However, in some cases the amounts producing insecticidal action in the blood of the host are at least below the dose producing gross toxic symptoms. This approach for controlling animal parasites warrants further exploration.

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COMMUNICATION TO THE EDITOR

Stockbridge, Massachusetts

April 13, 1949

Dear Doctor Adler:

Dr. Måhlon Ashford, Editor of the Bulletin of the New York Academy of Medicine has sent me your letter to him of April 8 in which you effectively contradict a statement I made in my article, "A Critique of the Present Status of the Psychotherapies" in the February (1949) issue of the Bulletin.

My statement, which appeared on page 111 of this issue, was "This (Adler's Individual) psychology and system of therapy died out with its leader." You point out that there are three institutes of Individual Psychology in the United States—New York, Chicago, and Los Angeles—and that there are a number of other evidences in this country and Europe that Individual Psychology is quite alive. Obviously I was mistaken on this point. I gladly retract the statement and extend my apologies. Also I have requested Doctor Ashford to publish my retraction.

Sincerely yours,

ROBERT P. KNIGHT, M.D.

RPK/hh

Dr. Alexander Adler
Individual Psychology Association N. Y., Inc.
333 Central Park West
New York 25, New York

ANNOUNCEMENT

Due to the rise in the cost of printing and paper, The New York Academy of Medicine finds it necessary to increase the subscription rate for THE BULLETIN, effective 1 August 1949 to \$5.00 a year for subscribers in the United States, Canada and Cuba.

THE EDITOR

BULLETIN OF THE NEW YORK
ACADEMY OF MEDICINE

CONTENTS

Iron Metabolism and Hemochromatosis	403
<i>S. Granick</i>	
The Present Status of Vitamin B ₁₂ in Pernicious Anemia	429
<i>Edward H. Reisner, Jr.</i>	
Pain in the Lumbosacral Region	434
<i>Jefferson Browder</i>	
Clinical Research Meeting	441
In Memoriam:	
Eugene Hillhouse Pool—1874-1949	466
<i>Frank J. McGowan</i>	
Announcement: Twenty-Second Graduate Fortnight	470

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MAHLON ASHFORD, *Editor*

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BULLETIN OF
THE NEW YORK ACADEMY
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JULY 1949

IRON METABOLISM
AND HEMOCHROMATOSIS*

S. GRANICK

Associate, Rockefeller Institute

THIS review will be divided into four parts. In the first part we will enumerate and classify the iron compounds of the body. In the second part we will describe the properties of some of these iron compounds. In the third part, the properties and the hypotheses concerned with the regulation of iron absorption by the gastro-intestinal mucosa will be discussed, and in the last part we will consider certain of the aspects of iron metabolism as they might be related to hemochromatosis.

I. IRON COMPOUNDS OF THE BODY

No detailed analyses exist for all the different iron compounds of the human. However, by incorporating various data from the literature, an approximate notion may be obtained of the distribution of total body iron among these various compounds. The iron compounds of the body may be divided into two groups. The first group will include the iron porphyrin or heme compounds and in the second group will be included the non-heme iron compounds (Table I).

The iron porphyrin heme compounds will be considered here very

* From the Laboratories of The Rockefeller Institute for Medical Research, New York. Read December 3, 1948 in the Friday Afternoon Lecture Series of The New York Academy of Medicine.

TABLE I: APPROXIMATE COMPOSITION OF THE IRON-CONTAINING COMPOUNDS IN THE HUMAN (70 KILO MAN)*

<i>Compounds</i>	<i>g.</i>	<i>Fe in g.</i>	<i>Per cent of total Fe</i>	<i>Reference No.</i>
Iron porphyrin (heme) compounds:				
Blood hemoglobin	900	3.0	60-70	(2)
Muscle hemoglobin (myoglobin)...	40	0.13	3.0-5.0	(1, 2)
Heme enzymes:				
Cytochrome c	0.78	0.004	0.1	(2)
Cytochrome a ₃ , b	—	—	—	
Catalase	—	—	—	
Peroxidase	—	—	—	
Non-heme iron compounds:				
Iron monomolecularly dispersed:				
Ferrous ion	—	—	—	
Siderophilin (Fe+++)	10.0	0.004	0.1	(4, 5, 6, 10)
Iron in micellar ferric hydroxide units:				
Ferritin	2.0-4.0	0.4-0.8	15	(7, 8)
Non-crystallizable ferritin	—	—	—	(7, 8)
Hemosiderin	—	—	—	(7, 8)
Total Iron				
		4-5	100	(1)

briefly. The essential function of the heme compounds when they are associated with particular proteins is to make oxygen available to the cell. We may best see how this is accomplished by following oxygen on its path into the cells. The oxygen in the lungs is taken up by the hemoglobin of the erythrocytes and transported to the tissues. In red striated muscle and heart muscle the oxygen is temporarily stored in muscle hemoglobin or myoglobin. Then the oxygen passes on in the cell to cytochrome oxidase (cyt.a₃), a heme enzyme which activates the oxygen to accept electrons. Other heme enzymes, as cytochromes c and b, serve to transport or shuttle electrons from organic compounds to the activated oxygen on the cytochrome oxidase. Another kind of heme enzyme, peroxidase, can activate H₂O₂ to act as a strong oxidant, and still another heme enzyme, catalase, can act to destroy toxic accu-

* The striated muscles of various animals, although not other tissues, appear to contain two non-heme iron fractions according to Dreyfus, Schapira and Leau, *Bull. Soc. Chim. Biol.*, 30, 99 (1948); one fraction, extractable by pyrophosphate may represent 30-90% of the total non-heme iron depending on the species. Assuming non-heme iron levels for muscle to be the same in human as in beef then for a 70 kilo man the total skeletal muscle would contain about 50 mg. and the heart about 12 mg. non-heme iron.

mulations of H_2O_2 which may be generated in the cell during these processes of oxidation with O_2 . It should be noted that the amount of iron in all of the heme enzymes of the cells is extremely small, being only a few tenths of one per cent of the total iron of the body. This is in marked contrast to the amount of iron in the hemoglobins of the red cell and muscle which together account for 65-75 per cent of the total body iron, assuming an average of 4.5 g. for total body iron.¹⁻⁸

The second group of iron compounds, namely, the non-heme group, is the one with which we shall be primarily concerned this afternoon. This group includes inorganic iron compounds and certain iron protein compounds (Table I). These compounds may be subdivided into two classes. The first includes the compounds of iron where the iron atoms are not in clusters—i.e. where the iron atoms are monomolecularly dispersed; the two substances that may be placed in this category are ferrous iron itself as a free ion and siderophilin, the β_1 serum globulin,—that is, the transport form of iron in the blood stream.

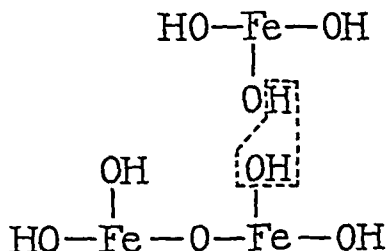
The second class of non-heme compounds contains iron in the form of ferric hydroxide units or clusters of a special character. The ferric hydroxide units are contained in ferritin, non-crystallizable ferritin and hemosiderin. These compounds containing ferric hydroxide units, serve as storage forms for iron. As one might expect from storage compounds, their content varies greatly from individual to individual."

Having briefly surveyed the various iron compounds of the body, let us now summarize the table on the approximate content of these compounds. Let us assume a total of some 4-5 grams for the iron in the body of a 70 kilo man. Then the total hemoglobin iron, i.e. in hemoglobin and myoglobin, accounts for the greatest fraction, 65-75 per cent, and ferritin iron makes up the next greatest fraction, about 15 per cent. Together these constitute about 85-90 per cent of the total iron. The other known constituents make up less than one per cent of the iron. There still remain, to be accounted for, about 10-15 per cent of the total iron of the body. Whether this latter amount of iron reflects errors in estimations, especially of total body iron or whether other compounds of significant iron content remain yet to be discovered, it is not possible to say.

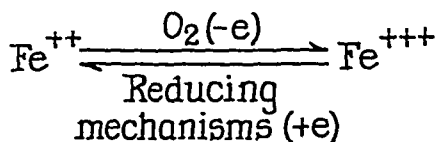
II. PROPERTIES OF THE NON-HEME IRON COMPOUNDS

Before discussing the properties of the non-heme iron compounds

two important properties of inorganic iron may be noted. The first is that iron may exist in the body in two states of oxidation, that is, either in the ferrous or the ferric state. The second is that the solubility of ferric ions is extremely slight. In contrast to the solubility of ferric ions, the solubility of ferrous ions, although low at body pH, is of significant magnitude. The reason for the very slight solubility of ferric iron is that the ferric iron is converted to ferric hydroxide at the pH of the body, and several ferric hydroxide molecules have a very great tendency to come together and split out water among them. In other words, the ferric hydroxide molecules aggregate or polymerize in three dimensions very readily into clusters or micelles of ferric hydroxide, thus:



Ferrous iron. We may look upon ferrous ions as the starting point from which all iron compounds of the body originate. Ferrous ions are only slightly soluble at body pH, but sufficiently soluble so that they may be reasonably considered to be an important metabolic intermediate. The solubility of ferrous hydroxide is equivalent to a concentration of 25 γ Fe per cent, but the ferrous iron may be made more soluble by the presence of bicarbonate or by loose complex formations with amino acids, etc. Unfortunately there is no adequate method for measuring the inorganic ferrous iron in the tissues. The reason for this difficulty becomes apparent when we realize that the level of ferrous iron is due to a dynamic equilibrium. In the presence of oxygen, ferrous iron tends to become oxidized very readily to the ferric form. There is, however, a tendency to reverse this process. The ferric iron is converted back to the ferrous form by the reducing mechanisms of the cell:



So the level of ferrous iron depends on the rate at which it becomes autoxidized directly by oxygen (or indirectly by oxidation catalysts) and the rate at which it is reduced back to the ferrous form. An understanding of the factors that are involved in the maintenance of this steady state, we believe, is basic to an understanding of hemochromatosis.

The second compound of this group of monomolecularly dispersed iron is siderophilin which serves as a transport form for iron (Cohn fraction IV-7). This protein molecule has been crystallized. It is a pseudo-globulin of molecular weight 90,000 that can carry two iron atoms in the ferric state. The protein is itself colorless. Schade and co-workers^{4, 10} have found that when ferrous iron is added to the colorless protein the iron becomes autoxidized to the ferric state and in the presence of CO_2 attaches to the protein. The protein now takes on a salmon-pink color. This pink complex contains one CO_2 for each ferric atom.¹⁰ The iron can be removed from the protein by adding a reducing substance to convert it to the ferrous state; or the ferric iron can be removed by lowering the pH to 4.6 (i.e. a less physiological expedient). It is important to note that no enzyme need be directly involved in the addition or removal of the iron to or from this protein. In the blood stream this protein is normally only about one-third saturated with iron, the serum iron level being about 100 γ per cent; when saturated with iron the serum iron level is about 300 γ per cent. It has been shown that the iron normally carried in the serum is carried exclusively by this protein. This protein may also carry copper, presumably at the same spots on the protein that would carry the iron.⁶ When the protein has copper on it, if one adds an iron salt, the iron will displace the copper. The constancy of the serum iron level is also indicative of a steady-state process. It therefore reflects various aspects of iron metabolism. We shall discuss this feature later.

The second class—the colloidal or micellar iron compounds—contain aggregates or polymers of ferric hydroxide. One of these substances is ferritin, and another of these is hemosiderin.^{7, 8}

Ferritin is a remarkable compound, first discovered by Laufberger in 1937. It is most readily isolated from horse spleen which is one of the richest sources of this substance. Ferritin is a brown iron-containing protein which can be crystallized readily by means of cadmium sulfate. In the crystallized state it may contain as much as 23 per cent dry weight of iron. One may remove the iron without damaging the

protein and the colorless protein, now called apoferritin, also will crystallize when CdSO_4 is added. So the property of crystallization is a property of the protein. The protein apoferritin has a molecular weight of 460,000.

Figure 1 is a hypothetical reconstruction of what a crystal of ferritin, containing 23 per cent iron, might look like. Here we see the somewhat ellipsoid apoferritin protein molecules and in the spaces we see ferric hydroxide micelles or clusters (cross-hatched spheres in the illustration) attached to the surface of the protein. Some cadmium atoms are represented as binding together the protein molecules possibly by coordinating certain amino acid groups on the surface of the two protein molecules.

The ferric hydroxide micelles of ferritin are not uniform in size, but are in general small enough to permit crystallization. Their average composition indicates that they contain about 1 PO_4 for every 9 iron atoms, i.e. $[(\text{FeOOH})_8(\text{FeOPO}_3\text{H}_2)]$. Theoretically, three types of ferric compounds are possible on the basis of the number of unpaired electrons which ferric iron may possess in the outermost electron shell. The ferric compounds may have either one, three, or five unpaired electrons per iron atom. The most common type of ferric compounds are those containing one and five unpaired electrons. An example of the type having five unpaired electrons is ferric chloride, or the iron in the transport compound, siderophilin; of the type having one unpaired electron an example is the iron in ferricyanide or in methemoglobin cyanide. These types are distinguished experimentally by making magnetic measurements to determine the number of unpaired electrons per iron atom. When ferritin was first measured by Michaelis, using the magnetic method, it was found that ferritin contained three unpaired electrons. The type having three unpaired electrons per iron atom is very rare. In the organism, ferritin iron can be distinguished from all other iron compounds since only ferritin iron has three unpaired electrons. Now the few experiments that have been done on the formation of these micelles or polymers indicate that these iron hydroxide units are polymerized through the mediation of some enzyme activity. It seems likely also that the individual micelles are attached to the apoferritin molecule through enzyme mediation. Support for the idea that an enzyme is involved in the formation of these micelles is the peculiar three-unpaired electron type, a type which we have been

unable to duplicate by *in vitro* experiments.

Ferritin may be considered to have three functions. Its primary function is that of a normal iron storage protein of the body. Many different tissues of the body appear to be able to make ferritin. Normally, ferritin may be isolated from the spleen, liver and bone marrow of a number of animals and in lesser amounts from testicles, ovary, kidney and pancreas. Agner has reported traces of ferritin in horse erythrocytes.¹¹ When the iron arriving in a tissue becomes relatively great, even a tissue like heart muscle which normally may contain very little or no ferritin, will be found to contain ferritin. Ferritin produced by the cells of one tissue, say the liver, is immunologically identical with ferritin produced by cells of other tissues of the body. From the average human liver one may isolate about $\frac{1}{2}$ to 1 gr. dry weight of ferritin; because of the inefficiency of isolation it may be estimated that twice this amount may be present.*

The second function of ferritin is related to the regulation of iron absorption. The mucosal cells of the gastro-intestinal tract control the amount of iron absorbed. The formation of ferritin in these mucosal cells is in some way connected with the production of a mucosal block in the mucosa, preventing excessive absorption of iron. Vosburgh and Flexner¹² have recently found ferritin in the human placenta and it seems likely that the placenta may also contain a mechanism similar to that of the intestinal mucosa, for the regulation of the iron absorbed by the embryo from the mother.

A third action of ferritin, and one which may be important in an understanding of irreversible shock, hypertension, edema, etc., has been recently revealed by Mazur and Schorr.¹³ This is concerned with the vasoconstrictor action of adrenalin. By the method of Zweifach and Chambers¹⁴ one may observe under the microscope the effect of the vasoconstrictor action of adrenalin on the terminal arterioles of the rat meso-appendix. When extremely small amounts of ferritin are added in the presence of adrenalin, the vasoconstrictor action of adrenalin is inhibited. In normal serum, ferritin appears to be absent or at least below the threshold sensitivity of this delicate test. However, in traumatic shock or in patients with liver cirrhosis, traces of ferritin may escape from the injured cells into the serum. The presence of the

* One of the highest and one of the lowest values for ferritin were found in two cases of leukemia. In one case of cirrhotic liver the ferritin crystals which were obtained in small quantity were pale yellow in color and contained only 5 per cent instead of the usual 20-23 per cent iron.⁹

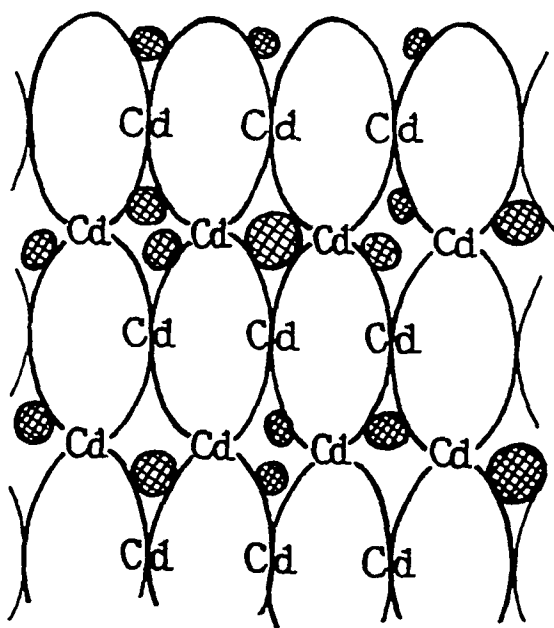


Fig. 1—Hypothetical reconstruction of a cross section of a ferritin crystal

ferritin in such serum can be demonstrated by its vasodepressor activity in the meso-appendix test. That it is ferritin and not another component of the serum which is active can be shown by adding antibody directed against ferritin. Then no vasodepressor activity is observed, that is, the vasodepressor activity of ferritin is counteracted by neutralization with its specific antibody. The effect of the ferritin is not due to its iron content since apoferritin will produce the same vasodepressor action as ferritin. The rat will respond to ferritin obtained from other species than its own, so it seems that there are common groupings on the protein that are responsible for the vasodepressor activity. The practical consequences of such a vasodepressor activity of ferritin and its control are clearly apparent.

When ferritin is crystallized out, there still remains in the mother liquor a brown pigment, called non-crystallizable ferritin. This has the characteristics of ferritin except that it will not crystallize. The evidence suggests that in this fraction the iron hydroxide micelles on the surface of the protein may be too large to fit into the crystal lattice (Fig. 1).

Hemosiderin is a granular substance which contains clusters of iron hydroxide units mixed with some protein material. These granules are

large enough to be microscopically visible and they stain for iron. The hemosiderin granules, separated from horse spleen, may contain as much as 35 per cent by weight of iron. This iron seems to have the same magnetic properties as ferritin iron or to deviate only slightly from it, indicating that the way the iron hydroxide units polymerize is probably identical with the way ferritin iron is polymerized. One might picture the formation of hemosiderin as an abnormal stage of iron deposition beyond that of ferritin. Ferric hydroxide micelles attached to ferritin, instead of consisting of small polymers might grow abnormally large. At the same time, cross-links between these enlarged ferritin molecules could take place (i.e. a cross-link could be formed by splitting out H_2O between two ferric hydroxide polymers on the surface of two separate ferritin molecules). It should be noted that the iron contained in these large clusters is less readily available to the body than is the iron of ferritin. The iron of ferritin is in minute clusters with relatively large surface area, such iron being more readily brought into solution by the reducing processes of the cells.

A reasonable view regarding hemosiderin formation is that if iron enters too rapidly into a tissue for apoferritin synthesis to keep pace with the entry of iron, or if a tissue is already saturated with ferritin, then this iron gets heaped up into granules. It is generally true that when one finds hemosiderin granules, one will find a high concentration of ferritin. However, one should not consider the hemosiderin granule as a normal storage form merely because it is microscopically visible. Ferritin is not microscopically visible nor can it be readily detected by iron stains because the ferritin is too diffuse in the cells, yet the iron of ferritin may be present in a decidedly higher concentration in the cell than is represented by the visibly stainable iron of the hemosiderin granules.

There is another form of microscopically stainable iron that might be confused with hemosiderin. This is the iron released from denatured hemoglobin. When red cells are damaged and engulfed by phagocytes, some of the material of the red cells is temporarily converted to denatured hemoglobin granules. These granules, lying in the digestive vacuoles of the phagocytes, first appear yellow-brown, the color being due to ferric hydroxide which is stainable, and to yellow bile pigment. Within 3-4 days the iron staining may disappear although some of the partially digested protein granules may still be tinged pale yellow due

to absorbed bilirubin. The iron may be carried away from the phagocytes by way of the blood stream and stored for example, in the liver. Or cells adjacent to these phagocytes may absorb the iron and convert it to ferritin iron if the cells have such an ability. For example, as seen in the dog, the slight hemorrhage resulting from release of a graafian follicle gives rise to a brown area in the vicinity of the corpus luteum from which ferritin has been crystallized.

In one experiment, an abnormal form of iron has been encountered. Normally, as shown in dogs,¹⁵ when a ferric salt is injected into the blood stream, it is absorbed rapidly by the liver and its five unpaired electron type is converted to the three unpaired electron type characteristic of the ferric hydroxide micelles of ferritin. In one instance this conversion did not take place and it can only be concluded that the enzymes which normally would convert this ferric iron were not functioning properly, that is, the dog may have been ill. Ferric iron, which is not handled properly, is toxic, and we shall discuss further on how a similar situation, arising in hemochromatosis might result in liver damage.

III. REGULATION OF IRON ABSORPTION

In contrast to the traces of iron that are needed to satisfy the heme enzyme requirements of simple forms like yeast, one may place the relatively enormous iron requirement of the mammal. This high iron requirement is due to the high content of hemoglobin in the mammal. In the body the iron contained in the hemoglobin of the red cells is about 3.0 grams. This is about one thousand times more iron than is used for the manufacture of all the heme catalysts of the body combined. In order to obtain an adequate amount of iron for hemoglobin synthesis, mechanisms had to be developed by the vertebrates for accumulating and regulating these biologically huge quantities of iron.

Absorption in the form of ferrous iron. The stomach has an important action on the iron ingested with the food. The stomach is acid, and this acidity or lowered pH has two effects. First, it converts colloidal ferric hydroxide of foodstuffs into monomolecularly dispersed ferric ions. Second, at acid pH certain substances in the food act to reduce the ferric ions to the ferrous form. For example, ascorbic acid or cysteine or the -SH groups of proteins in food will not reduce ferric salts at pH 7, but reduction can already be observed at pH 5.

The reduction of iron to the ferrous form is of importance because it has been clearly demonstrated that it is in the ferrous form that the iron is absorbed.¹⁶

Although iron may be absorbed all along the gastro-intestinal tract, very little is absorbed normally except in the duodenal region.^{1,17} In the acid stomach the ferrous iron which is formed by reduction, is stable, that is, it is not readily autoxidizable by oxygen. In the duodenum there is present a most active region of absorptive surface and a pH which is still not much above 5. The region just below the pyloric sphincter will therefore be most effective in absorption of ferrous iron. As the iron moves further down the intestinal tract the digestive juices of the pancreas, bile and the intestinal mucosa tend to raise the pH to 6-7. At this higher pH the ferrous iron becomes rapidly autoxidizable and will be converted to ferric hydroxide. Normally with the relatively low content of iron coming in with the food, say 2 to 10 mg. Fe per day, the main absorptive region may be limited to a very short segment below the pyloric sphincter. If a larger dose of iron is given, say 50-100 mg. Fe, a larger region of the duodenum may be involved in absorption, and with still larger doses of iron as is suggested for use in iron deficiency anemia (300 mg. Fe^{++} , 3-4 times daily), more of the intestinal tract, perhaps even the large intestine and stomach, may absorb significant amounts of iron. Even under conditions of anemia and this high dosage, only about 15 mg. of a total of 300 mg. Fe^{++} may be absorbed. When a large dose of ferrous iron is fed to a hypochromic anemic the serum iron may rise to saturation level in 6 hours and drop down in 4 hours more to its original low level.¹⁸

When a dose of iron is first increased, it may be found that the efficiency of absorption of this dose will be relatively high because a new region of mucosa comes to take part in the absorption. However, it should not be considered that this efficiency remains high if this higher dose continues to be fed since a mucosal bloc would be rapidly established in this new region and again absorption would decrease.

Properties of the mucosal cell in the regulation of iron will now be discussed. In general, the organism may regulate a substance taken into the body by way of the gastro-intestinal mucosa in two ways. The organism may either absorb all of the particular substance such as K^+ or Na^+ into the blood stream and excrete the excess; or the organism may develop a mechanism for regulating the amount of the

substance which is to be absorbed. In the case of iron, a regulatory mechanism of great nicety, residing in the mucosa of the gastro-intestinal tract, was developed.* Two features of this regulation may be noted. In the first place, the mucosa behaves as if it knew how to maintain a low, relatively steady rate of absorption under normal conditions. In the second place, when the red cells are below their normal number, i.e., in anemia, the mucosa behaves as if it knew that it must respond by absorbing iron with greater efficiency.¹

For example, let us consider what is the amount of iron absorbed under normal conditions. An average meal may contain approximately 5 mg. Fe, of which only about 0.5 mg. may be absorbed. In other words, for this dose of iron the efficiency of absorption is about 10 per cent. This would mean that a maximum of about 1.5 mg. Fe per day would be absorbed. It has been estimated that the body may lose a total of about 1 mg. or less of iron per day.¹⁹ This loss is mainly due to the sloughing off of cells from the gastro-intestinal tract, including traces of iron lost in the bile and still smaller quantities lost in the urine. Thus the net gain by the body may be as much as 0.5 mg. of iron per day. The accumulation of 0.5 mg. of iron per day would be sufficient to care for the needs of even a growing child.¹ Considering the very approximate nature of these calculations one may say that on an average diet, the net gain in iron would serve for the manufacture of about 300-600 cc. of blood per year.

Suppose now that blood were lost by hemorrhage and that an anemia ensued. Then one would find, for example, that instead of only 10 per cent of the iron being absorbed, 50 per cent would be absorbed.

Let us next suppose that even though no anemia existed, the efficiency of iron absorption, instead of being 10 per cent, were increased to 30 per cent; then about 3.5 mg. of iron per day would accumulate. The result of this increased efficiency would be that over a 20-year period some 30 gm. of iron would be deposited in the body. Such an amount of iron is sufficient to produce symptoms of the disease called hemochromatosis. We see from this example, that whether the process of absorption is to be considered normal or abnormal may depend on relatively small differences in the level of efficiency with which iron is absorbed over a long period of time.

* Recently, Mitchell and Hamilton, *J. Biol. Chem.*, 178, 345 (1949) have reported an average daily excretion of 6.5 mg. Fe in male human sweat. This surprising finding, which according to these authors might make unnecessary the assumption of a mechanism for limiting iron absorption, awaits confirmation.

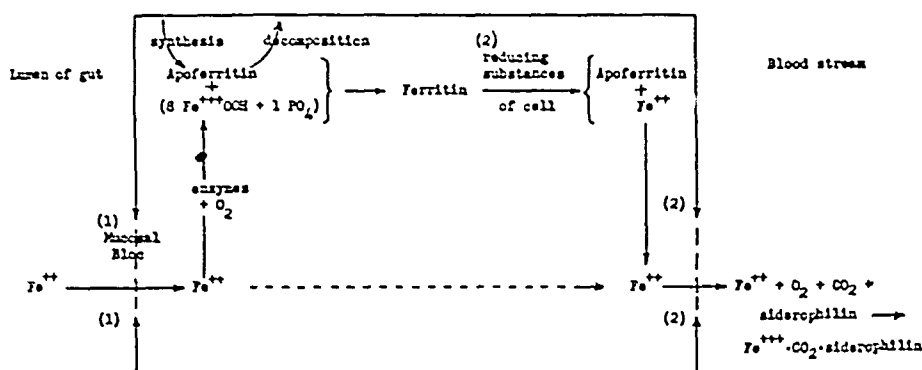


Fig. 2. Hypothesis of the regulation of iron absorption by the mucosal cell

(1) The amount of ferrous iron moving into the cell is regulated by a mucosal bloc related to the presence of ferritin.

(2) The amount of ferrous iron moving into the blood stream depends on the relative redox level of the cell and this in turn is a function of the amount of O_2 supplied by the blood stream.

We shall now consider the facts that reveal a regulatory mechanism for absorption of iron in the gastro-intestinal mucosa. (The diagram of Figure 2 may be useful in the following discussion.)

1. It can be shown that once iron gets into the organism it can no longer get out. For example, Widdowson and McCance²⁰ demonstrated in 1937 that iron injected into the blood stream in large doses was not excreted by way of the urine or feces. More recent experiments with radioactive iron have confirmed this observation. A dramatic demonstration of this fact is seen in a patient with hemolytic anemia who had some 200 blood transfusions over a period of several years. The iron from all of these broken-down red cells totalled about 25 gm. The patient developed hemochromatosis and died of the effects of this relatively huge deposit of iron in all of the tissues of the body including the heart muscle.

It follows, if iron cannot be excreted after absorption, that the movement of iron from the intestinal tract into the mucosal cell must be always in one direction, i.e., no iron can move out of the mucosal cell into the intestinal tract. So one of the properties that may be deduced from the non-excretion of iron is that the *mucosal cells must provide a one-way transfer of ferrous iron into these cells.*

2. Next it can be shown, that the mucosal cell must contain a mechanism which will regulate the amount of iron finally entering the blood

stream. The experiments of Hahn and others at Whipple's laboratory, performed on dogs with radio iron as tracer, have revealed this fact.^{1,21} If radioactive iron is fed to a normal dog, relatively little iron is absorbed. If radio iron is fed to a chronically anemic dog the iron is absorbed in an amount 5-20 times the amount absorbed by the normal dog. Other workers have confirmed this finding in humans. This experiment tells us first, that an *anemia can increase the absorption of iron into the blood stream*. Secondly, it tells us that *in the normal there is a resistance or mucosal bloc to iron absorption*.

3. Another experiment of Hahn and coworkers^{1,21} shows that there is a relationship between this resistance, or mucosal bloc, and the storage iron. When a normal dog was bled severely to produce an acute anemia the rate of iron absorption was found to be normal during a period of about a week. Only after this time was iron absorbed at a greater rate, that is, there was a lag in response to the anemia. This experiment suggests that during this early period, immediately after bleeding, the storage iron in the form of ferritin was being depleted to be utilized in the synthesis of new erythrocytes. Not only was the ferritin depleted in the liver, spleen and marrow, but the ferritin in the mucosal cells of the gastro-intestinal tract was also broken down. If the lag represents depletion of ferritin in the mucosal cells, then one should be able to demonstrate a change in ferritin content of the mucosal cells in response to the feeding of iron.

4. That the level of ferritin in the mucosal cells readily responds to the feeding of iron has been demonstrated in the guinea pig. In this animal ferritin is normally present only in traces in the mucosa. When high doses of ferrous iron are fed, ferritin is found to increase, especially in the duodenal region and then after a few days to decrease. In about 3-4 hours after feeding a dose of iron, a marked increase in ferritin takes place, reaching a maximum in about seven hours and declining after 2-5 days to normal. *One might postulate that the presence of ferritin was in some way connected with the presence of the mucosal bloc*, that is, only when ferritin in the mucosal cells was depleted would more ferrous iron be absorbed.

One may detect ferritin by the following simple procedure: Several centimeters of the duodenal mucosa of a guinea pig are scraped onto a slide and a few drops of 20 per cent CdSO_4 solution are mixed with this tissue. Then a cover slip is placed on it, and the liquid is permitted

to evaporate slowly overnight. Examination of the duodenal mucosa of the normal guinea pig in this manner reveals some tiny ferritin crystals. These crystals are quite rare and it is necessary to hunt for them with an oil immersion lens. However, if 10-20 mg. of ferrous iron are fed to a guinea pig and its duodenal mucosa is examined the next day, then several hundred ferritin crystals may be found on the slide. The highest concentration of ferritin is found in the duodenal region, less in the jejunum, and only traces in the ileum, large intestine and stomach.

It is a surprising fact that colorless crystals, i.e., of apoferritin, are not found in the mucosa. This protein crystallizes just as readily as it does when it has iron hydroxide micelles attached to it, i. e., apoferritin crystallizes as well as ferritin. If ferrous iron is fed, ferritin crystals can be demonstrated. This means that the feeding of iron in some way brings about an increase of a specific protein, apoferritin, to which the iron attaches in micelles of a particular kind of iron hydroxide, forming the compound, ferritin. A plausible way of looking at this phenomenon is to consider that apoferritin is constantly being synthesized and broken down. If iron hydroxide micelles attach to the apoferritin then the apoferritin is prevented from being broken down. Thus feeding of iron will lead to an accumulation of ferritin (Fig. 2).

Serum iron. Let us next consider how the serum iron reflects various aspects of iron metabolism and whether the serum iron level may be related to absorption of iron by the mucosal cells. A number of careful studies on this subject have come recently from the laboratories of M. M. Wintrobe¹⁹ and C. V. Moore.¹⁸ As has been noted before, the iron in the serum is transported by siderophilin, a β_1 globulin protein of molecular weight 90,000. Normally this protein is only one-third saturated with iron. If 10 mg. of ferrous iron are injected into the blood stream the serum iron can be raised from the normal value of about 100 γ per cent to about 300 γ per cent. Iron injected above this saturation level disappears very rapidly from the blood stream at the same time that toxic symptoms appear.^{5, 22} This excess iron probably precipitates out and is filtered off by the lymph glands and by phagocytes.

The serum iron under normal conditions will reflect the level of iron available for hemoglobin synthesis.^{23, 24} 1. The serum iron will be low in nutritional anemia (Table II) because there is too little iron

Hypothesis on the regulation of iron by the mucosal cell. I have now finished presenting what appear to me to be the known pertinent facts about the absorption of iron and its regulation. The problem of iron absorption and regulation is a part of the larger problem of selective absorption and permeability. We are most strikingly reminded of our ignorance of such processes when we consider the functioning of the mammary gland, where the blood stream abuts one side of the cell and from the other side milk issues forth. It may seem foolish to even attempt an hypothesis of iron absorption and regulation at this stage of our knowledge. But I am going to make this attempt to outline a hypothesis on iron absorption and regulation for the purpose of summarizing and bringing together the facts into some coherent scheme. If such a hypothesis can suggest some correlations or new experiments it will have served a useful purpose.

Any proposed hypothesis must explain the following facts: 1. There is a one-way transfer of iron into the mucosal cell from the gut. 2. There is a resistance or bloc to iron absorption in the normal. 3. In the normal, after an acute anemia, there is a delay of about a week in responding to the anemia by an increased iron absorption. 4. After an iron feeding there is a rapid increase in ferritin (over a period of several hours) in the mucosal cells and then a rather slow decrease in ferritin (over a period of several days). 5. Apoferritin protein increases in the mucosal cells when iron is fed. 6. The chronically anemic condition brings about a greater absorption of iron.

The hypothesis is outlined in the scheme presented in Figure 2. We are going to postulate that a gradient of reduction exists in the cell, that portion of the mucosal cell closest to the lumen of the gut being less reducing for ferric iron, and that portion closest to the blood stream having a higher reducing ability for ferric iron. No direct evidence, however, exists for this assumption.

According to this hypothesis the iron would be absorbed in the ferrous form from the lumen of the gut into the mucosal cell. This passage is one-way. Once the iron enters the cell it never passes back again through this membrane. One possible explanation for this one-way movement might be that the ferrous iron once in the cell is rapidly oxidized and incorporated into ferritin. This would mean that the ferrous iron is perhaps enzymatically converted to the special 3-unpaired-electron type of ferric hydroxide polymer. Apoferritin protein mole-

cules may be postulated to be constantly turning over, i.e., being formed and broken down. When the ferric hydroxide polymers attach to the protein to form ferritin, the ferritin is stabilized so that the feeding of iron would lead to the accumulation of the iron hydroxide protein compound, ferritin.

Whether ferritin is directly connected with the mucosal bloc* or whether the presence of ferritin merely indicates that the cell is saturated with respect to some iron compound more closely allied with the mucosal bloc cannot be decided.

At the blood stream end of the cell, it is postulated, the ferric iron of ferritin is reduced to ferrous iron by the reducing mechanisms of the cell and enters the blood stream to be autoxidized to the ferric state and attached to siderophilin in the presence of CO_2 . The concentration of siderophilin does not appear to affect the rate of movement of iron from the mucosal cell into the blood stream.

In uncomplicated iron deficiency anemia and other anemias, such as pernicious anemia, pyridoxine deficiency anemia, etc., the iron is absorbed more effectively into the blood stream. In these anemias the common feature appears to be a low oxygen supply in the tissues brought about by a low hemoglobin content of the blood stream. The low oxygen supply would lead to a relatively anaerobic atmosphere in the mucosal cell and might bring about a faster rate of reduction of ferric ferritin to ferrous iron and thus more ferrous iron might leave the cell.

According to this hypothesis, two mechanisms take part in regulating iron absorption in the mucosal cell. One is the mechanism of the mucosal bloc which is directly or indirectly connected with the ferritin content of the mucosal cells. The mucosal bloc may be regarded as a response to the cell being saturated with some iron compound. The second mechanism regulating iron absorption is postulated to be connected with the so-called "redox" level of the cell. The reducing systems are pictured as converting the ferric hydroxide micelles to ferrous iron, the ferrous iron then diffusing into the blood stream. In anemic conditions, the lower oxygen content in the mucosal cell would favor the reduction. Thus ferrous iron, absorbed from the gut might

* How can the presence of ferritin diminish the uptake of iron by the mucosal cell? One suggestion, purely hypothetical, is that some substance necessary for iron absorption in the cell might be removed from the cell and stored as ferritin. Only when the ferritin is broken down and the iron released would this substance be released.

stay in the ferrous form and move directly through this cell in this form. If conditions were normal, ferritin might be stored up and the bloc to further iron absorption would then be established.

IV. HEMOCHROMATOSIS

Hemochromatosis is a disease characterized by an extensive deposition throughout the body of ferric hydroxide polymers in the form of brown iron-staining granules. These iron-staining granules are called hemosiderin granules. The deposition of hemosiderin may be especially marked in the liver and pancreas. The spleen and bone marrow contain relatively little of the pigment.^{38, 39}

This iron-containing pigment is also accompanied by another pigment devoid of iron, called "hemofuscin." Hemofuscin may vary in color from gray to yellow to brown. It is very poorly characterized and may well represent several different substances, produced in the same or different cells as a result of abnormal cell metabolism.

Hemochromatosis is an interesting disease to students of iron metabolism since this disease appears to be a disorder connected with the absorption of abnormally large amounts of iron. Normally the total body iron may average 4-5 grams. In hemosiderosis the liver alone may contain 20 or more grams of iron. This accumulation of iron may be due to only a relatively slight increase in the efficiency of iron absorption as compared with the normal, since the excessive accumulation may be a process that goes on over a period of 20-30 years before it is detectable. As has been mentioned before, in order to accumulate some 30 gm. of iron over a period of 20 years as in cases of hemochromatosis, it would be necessary to accumulate about 3.5 mg. of iron per day, i.e., instead of the absorption of iron, from a meal containing 5 mg. Fe, being only 10 per cent efficient it would have to become 30 per cent efficient.

The first organ to be generally affected is the liver. This organ is the primary storehouse for iron, the iron being normally present as ferritin. If iron continues to be brought to the liver the following sequence of events may be postulated: The liver will form ferritin up to its capacity. The excess iron probably will continue to deposit on the already existing micelles increasing their size, and the links between micelles will tend to unite ferritin molecules to form clusters that eventually become large enough to be visible under the microscope (i.e.,

the hemosiderin granules). At the same time a portion of this iron may begin to spill over into other organs to be converted to ferritin and the excess finally to be deposited in the form of hemosiderin.

This process of iron deposition which is postulated to take place is probably normal in so far as the iron is converted to the normal 3-electron type of ferric hydroxide.¹⁰ It has not been demonstrated that huge accumulations of iron in the form of ferritin and hemosiderin by themselves will bring about cell destruction with consequent fibrosis. Rather does it seem more reasonable to consider that iron which is not converted to the proper kind of ferric hydroxide may bring on cell destruction by precipitating proteins indiscriminately or perhaps by inactivating one or more specific enzymes.* If an acute inflammatory disease should arise in a subject whose liver is laden with ferritin and hemosiderin it is possible to conceive that the cells will not handle the iron properly at this time; and an excessive amount of an improper form of iron may then injure or irreversibly damage the cells. Another factor to be considered in hemochromatosis where ferritin is very high, is that injury to the liver may cause ferritin to escape into the blood stream leading to vasodepressor action of ferritin and its sequelae.

What factors may one postulate which might cause an excessive deposition of iron?

1. An accumulation of iron may be brought about as a normal response to a lowered oxygen supply. For example, in nutritional anemias such as in pyridoxine deficiency, pernicious anemia, copper deficiency, nicotinic acid deficiency, etc., the mucosal cells respond to the anemic condition in a normal manner, by permitting a greater than normal amount of iron to enter. In hemolytic anemia also, a greater amount of iron will enter than in the normal. Mallory¹² has claimed that a hemolytic anemia arising from chronic poisoning with copper might lead to hemochromatosis. Although iron derived from hemolysis would be found in especially large amounts in the spleen and bone marrow, it is possible that a redistribution of iron will occur over a period of years so that if a low grade hemolytic anemia had once been present and eventually disappeared one might not be able to recognize the fact by studying the tissues of the hemochromatosis case.

2. The hemochromatosis may be brought about as a result of ad-

* For example Racker and Krimsky¹¹ have called attention to the inhibitory action of iron on the important triose phosphate dehydrogenase enzyme.

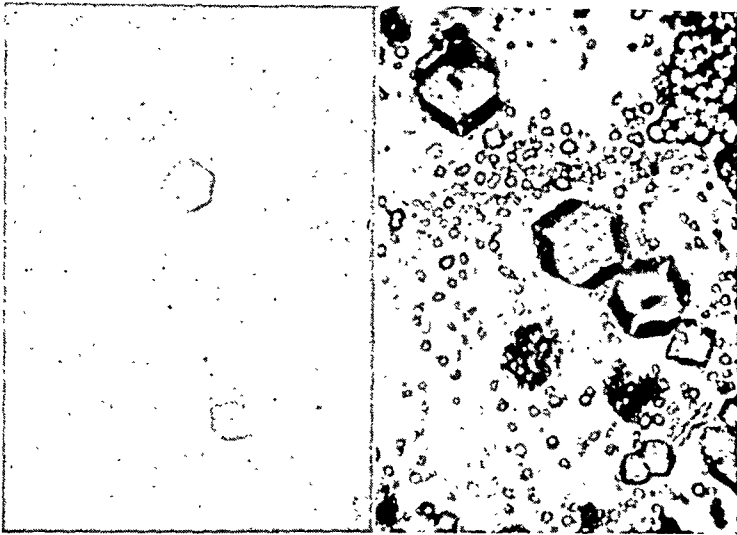


Fig. 3A

Fig. 3B

A. Ferritin crystals from human duodenal mucosa of case of hemochromatosis.

B. Ferritin crystals from liver of a case of hemochromatosis brought on by a large number of transfusions.

ministering a large number of transfusions to a patient with hemolytic anemia. In one such case, after administration of about 200 blood transfusions the patient eventually died of hemochromatosis resulting from the iron liberated from the transfused blood. The liver was found to be extremely rich in iron and well developed crystals were obtained (Fig. 3B). The heart muscle also was found to contain ferritin. Schwartz and Blumenthal³⁹ have recently reviewed a number of such cases. They have noted that often the number of transfusions administered was too small to account for the high iron content of the tissues. This suggests that the anemic patients over a period of years had absorbed large amounts of iron in response to the anemic condition. The additional accumulation of iron from transfusions of blood seemed to bring out the symptoms of hemochromatosis.

3. Hemochromatosis may also be brought about by an inborn error of metabolism in the mucosal cells. Sheldon³⁸ has presented some evidence that this metabolic error may be inheritable. Lawrence⁴³ has described a family where the mother and two sons died of typical hemochromatosis, two sons had borderline cases, and two other sons

and three daughters were not affected.

The blood values in hemochromatosis are not abnormal, averaging about 4.1 million R.B.C. and 80 per cent hemoglobin. A diagnostic sign of hemochromatosis is the high serum iron, the siderophilin protein being saturated with iron. Overcoming certain objections to previous techniques, Dubach et al²² in an excellent study, have described a case of hemochromatosis in which a test dose of 70 mg. of ferrous iron was fed by mouth. Of this test dose 20 per cent was retained by the hemochromatosis patient whereas the normal would retain 2 per cent or less of such a dose. This is the first direct evidence demonstrating that in hemochromatosis iron absorption is greater than normal.

Where does the abnormality lie in the mucosal cell which is responsible for hemochromatosis? We can examine this question only in the light of our limited knowledge. In terms of the hypothesis presented above (Fig. 2), two metabolic processes may govern the regulation of iron absorption by the mucosal cell. One is the sequence of reactions characterized by the mucosal bloc and related to ferritin turnover. The second is the process connected with the reducing ability of the cell.

If the processes related to the mucosal bloc are responsible it might be possible to show that some defect may be present that is connected with ferritin formation. We have examined the tissues of a case of typical hemochromatosis (i.e., cirrhosis of the liver, fibrosis of the myocardium) kindly provided us by Dr. R. West, with the idea that if the mucosal bloc were at fault then the mucosa might not form ferritin.⁴⁰ This idea proved to be incorrect. Ferritin crystals were obtained from the mucosa (Fig. 3A) and relatively huge amounts of ferritin were isolated from the liver. This indicates that no defect is present in this particular case of hemochromatosis, either in the formation of the iron hydroxide micelles which were of the characteristic 3-unpaired electron type, or in the enzymes connected with apoferritin and ferritin formation. The finding of ferritin in the mucosa makes it less likely that factors in the mucosal bloc may be involved.

It seems more likely that the metabolic error in hemochromatosis might be due to a slightly greater reducing tendency of the cell for iron. This would permit somewhat more iron to pass to the blood stream than in the normal. The greater reducing tendency or lower "redox" level might arise either by an increased effectiveness of the reducing enzymes or might be brought about by a decrease in the effectiveness

of the oxidizing enzymes.

To the practicing physician the practical question must be uppermost. What can be done for a patient with hemochromatosis? Little hope can be extended to a far-gone case except symptomatic treatment of cirrhosis, or the diabetes or heart involvement.

However, there would seem to be already a rational approach to the prevention of hemochromatosis. The hemochromatosis of the nutritional variety is probably extremely rare in this country. We are then concerned primarily with the hemochromatosis due to metabolic error.

1. Prevention and treatment depend on an early recognition of the development of this disease. A diagnostic sign is a rather high serum iron and an otherwise normal blood picture. If near relatives have had hemochromatosis there is all the more reason to be suspicious.

2. A diet might be considered which would limit iron absorption first by complexing the iron and secondly by keeping iron in the ferric state. A diet high in phosphates especially in phytic acid would render the ferric iron highly insoluble. One might consider increasing the oxidizing activity of the diet by adding vitamin K as the naphthoquinone. One might also decrease the intake of ascorbic acid in the food during meals to prevent the ferric iron of the food from being reduced.

3. One might consider the feasibility of making the potential hemochromatosis patient a regular blood donor since bleeding would be the only direct way of removing accumulations of iron from the body. In hemochromatosis developed to the stage of liver or pancreas involvement, however, this procedure might not be advisable.

4. An aim of the future, would be to study the metabolism of the mucosal cell in order to understand the factors governing the reducing mechanisms of the cell. Eventually one might attempt to control this activity by blocking one or another enzyme with some enzyme inhibitor or anti-metabolite.

In this talk I have attempted to summarize some of the aspects of our knowledge and hypotheses of iron metabolism and to relate them to the disease, hemochromatosis. The advances in our knowledge and changes in our viewpoint have been so great within the last 10-15 years that an important book on iron metabolism in relation to hemochromatosis by Sheldon, published in 1936, reads today like ancient history. I

hope that this rapid pace for advancing our knowledge of iron metabolism will continue and that this material which I have presented to you this afternoon will in turn shortly have the hollow ring of ancient history.

I should like to express my gratitude to Dr. L. Michaelis for his criticisms of this paper and his constant interest.

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THE PRESENT STATUS OF
VITAMIN B₁₂ IN PERNICIOUS ANEMIA *

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WINTROBE states in his book, *Clinical Hematology*—"A confusing array of 'B vitamins' . . . have been shown to be related to blood formation." In the past pyridoxine, riboflavin, nicotinic acid and folic acid have been shown to play a role in hematopoiesis, and now vitamin B₁₂ has been added to that group. It is the purpose of this paper to review briefly the steps leading up to the discovery of vitamin B₁₂, to discuss some of the facts we now know about it, and to show you the records of cases treated with it by Randolph West and myself.

Ever since the discovery of the effect of liver in pernicious anemia, successively more potent extracts of liver have been produced in the effort to isolate the active antianemic principle. These attempts were retarded by the necessity to test the potency of liver fractions by tedious clinical trial methods. With the discovery of folic acid a new technique of bioassay was developed, depending on the fact that certain bacteria required folic acid to achieve optimum growth. In 1947 Shorb¹ reported that the growth requirements of *Lactobacillus lactis* Dorner for liver extracts paralleled their antianemic potency. This provided an in vitro method of testing the potency of such extracts and expedited the research culminating in the isolation from liver last year by Rickes and his associates² of some reddish crystals, designated vitamin B₁₂. Simultaneously, the same substance was isolated by English investigators under Smith,³ using the traditional clinical test methods.

Vitamin B₁₂ is a red crystalline substance with a molecular weight of 1630.⁴ It contains cobalt, nitrogen and phosphorus but no sulphur.⁵ It is extracted from liver in exceedingly small amounts and can also be obtained from a variety of sources in nature, including the manure of cows, chicks and other species⁶ and has recently been reported to be found in the liquor produced in the production of streptomycin. Its potency in the treatment of pernicious anemia was reported by West⁷

* From the Fourth Medical Division (New York University), Bellevue Hospital, N. Y. Given February 15, 1949 before the Section on Medicine of The New York Academy of Medicine.

and confirmed shortly by Spies⁸ who also found it effective in sprue and nutritional macrocytic anemia. Its outstanding feature was its potency, doses as small as 4 micrograms being adequate to produce a maximal reticulocyte response.

The first patient treated was a 66 year old white female with pernicious anemia, a patient on the wards of the Kings County Hospital, made available to Dr. West through the courtesy of William Dock. Following a single injection of 150 micrograms a maximal reticulocyte response of 27 per cent was observed and the blood count rose to normal and is still over four million, ten months later, with no further therapy.

Having established the efficacy of the material, a series of trials was instituted to establish the limits of potency, using patients on the First and Fourth Medical Divisions of Bellevue Hospital. It was found that a single injection of as little as 3 to 6 micrograms produced a maximal reticulocyte response, and a total dose of 56 micrograms in one patient effected complete hematologic remission, which was maintained for four months before relapse, with no additional therapy. A dose of one microgram a day was found to give a maximal reticulocyte response and restore the blood count to normal. A daily injection of $1/10$ of a microgram was ineffective, but remission occurred when this was increased to $3/4$ of a microgram daily. One-half a microgram daily gave a submaximal reticulocyte response. From these experiments the unit potency of B_{12} was fixed at approximately one unit per microgram, a unit being defined as the amount of antianemic substance required daily to effect and maintain hematologic remission in a patient with pernicious anemia.

The next problem to investigate was the effect of B_{12} on the neurologic lesions of combined sclerosis. One of the Bellevue patients had exhibited early cord lesions at the onset of treatment with one gamma a day, and at the end of fifty-three days of treatment had a negative neurological examination. Four patients with more severe neurological disease were treated at the Columbia-Presbyterian Medical Center by Dr. West. The dose employed here was 25 micrograms a week. There was marked improvement in ability to walk, and gain in subjective and objective motor strength and coördination. The neurologic signs such as Babinski and Romberg signs tended to diminish or disappear. Vibratory sense on the other hand improved slowly and only slightly. These

patients have now been followed for eight months, and on 25 micrograms a week have maintained their improvement and shown no sign of relapse. In general the neurological results of treatment with B₁₂ seem to be as satisfactory as those that might have been obtained with vigorous liver therapy.

Meanwhile other workers have been investigating various aspects of B₁₂ treatment and reporting their findings which will be briefly summarized. Hall⁹ reported beginning disappearance of megaloblasts from the bone marrow as early as 18 hours after the injection of B₁₂. Bethell¹⁰ demonstrated that a substance probably the same as B₁₂ was excreted in the stools of patients with pernicious anemia in relapse, and that this substance when extracted from their stools and given parenterally, caused remission. Berk et al¹¹ reported that when B₁₂ was given by mouth it was ineffective unless gastric juice was given with it, an observation confirmed by Hall.¹² From these facts it has been suggested that the role of the intrinsic factor of Castle may be to promote the absorption of B₁₂ from the gut, and B₁₂ has been suggested to be the extrinsic factor.

The question will at once be asked about the relationship of B₁₂ to folic acid. Bethell¹⁰ reported that the response to B₁₂ was inhibited by folic acid antagonists. Sturgis¹³ has reported that B₁₂ is ineffective in the so-called pernicious anemia of pregnancy, which is cured by folic acid, and Luhby reports that B₁₂ is likewise ineffective in the treatment of acute megaloblastic anemia of infancy, which also responds to folic acid. Folic acid and B₁₂ probably operate at different levels in the process of hematopoiesis.

It has been shown that thymine in a ratio of several thousand to one can replace folic acid in the growth requirements of *Streptococcus lactis* R¹⁴ and *Lactobacillus casei*.¹⁵ Spies¹⁶ gave thymine in similarly large doses to patients with pernicious anemia and sprue, and obtained restoration of the blood count. Like folic acid, however, thymine had no effect on the neurologic lesions in these conditions.¹⁷ Wright¹⁸ has shown that the growth requirements of *L. lactis* can be met by substituting thymidine for B₁₂ in a ratio of 10,000 to 1. Thymidine is the desoxyriboside of thymine and from the foregoing evidence it is tempting to postulate that the role of folic acid is to act as a coenzyme in the formation of thymine, which is then converted to its desoxyriboside by the enzymatic action of B₁₂. We have attempted to treat patients

with pernicious anemia with thymidine in dosage up to 150 micrograms, without notable effect. While such an hypothesis is attractive it is probably oversimplified and fails to take into account a wealth of accumulated evidence concerning the role in hematopoiesis of other factors, including xanthopterin,¹⁹ and other pterins. Most recently a highly potent hematopoietic substance called B₁₄²⁰ has been announced, but this claim is awaiting confirmation at present.

Finally, the presence of cobalt in B₁₂ is certain to excite interest because of the fact that this element has been implicated for many years in the production of experimental polycythemia.²¹ With the aid of its isotopes it is now possible to learn more about the fate of cobalt in the body,²² and the presence of this inorganic ion in B₁₂ may ultimately be of great help in studying the formation and role of this vitamin. Two of our patients were treated by West with cobaltous chloride with no effect, before they responded to B₁₂.

To summarize, it would appear that vitamin B₁₂ is identical with the long sought anti-pernicious anemia fraction of liver. It has an anti-anemic potency of one unit per microgram of crystalline substance, and brings about complete hematologic remission, and improvement of the neurological lesions comparable to that obtainable with liver. In the light of recent observations it would appear that our twenty-year-old concept of extrinsic and intrinsic factors in pernicious anemia may have to be modified, and to end in the vein in which I started, the "array of B-vitamins" has been extended, and the confusion, which I have tried tonight to dispel to some extent, is still very dense.

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PAIN IN THE LUMBOSACRAL REGION*

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BACKACHE both with and without radiation of pain into the lower extremities is an exceedingly common complaint. It impairs the efficiency of thousands of manual workers, curtails the activities of some seeking physical recreation and accounts for the acid disposition of many an otherwise pleasant housewife. Last year alone, some 2200 patients with pain in the lower back were considered by the officials of the New York State Industrial Commission and other thousands consulted orthopedic surgeons, neurosurgeons, osteopaths and chiropractors. The fact that many of these wander from doctor to doctor as well as to members of legally unrecognized healing cults clearly indicates that we are as yet incapable of determining the nature of many of the lesions that produce pain in the lower part of the back and that there is no specific therapy for a large number of these sufferers. To label such complaints as sacroiliac strain, arthritis, or one of a host of other appellations that mean nothing and certainly bring little, if any, help to the patient, tends to terminate investigation that may eventually lead to a correct diagnosis. It seems best that the "book be kept open" for those with backache of undetermined cause, and gradually, as in the case of herniated intervertebral disc, other clinical syndromes may be delineated from the stock pile of patients with low back pain.

It is therefore appropriate to first consider the syndromes characterized by pain limited to the lower back. In most instances the pain is relatively sudden in onset, usually precipitated by physical exertion and often aggravated by any movement of the lower vertebral column. Frequently the patient states that at the outset "something tore loose in my back" or "something slipped out of place." In others, the initial discomfort is relatively mild but after a night's rest they are unable to get out of bed or, once up, are unable to dress themselves. Those so

* Read November 5, 1948 in Friday Afternoon Lecture Series at The New York Academy of Medicine.

afflicted walk with a cautious gait and many have a slight limp. The trunk may be tilted forward or laterally and the upper extremities may be carried in slight abduction to aid in balance. Difficulty in arising from a sitting position is common and to retrieve an object from the floor is impossible. The pain is described as a continuous boring ache deep in the middle of or to one or the other side of the lumbar region of the back. During periods of exacerbation the pain tends to spread over the buttocks and into the upper thighs. Lying supine on a hard surface usually gives considerable relief. Examination is usually not very enlightening. The normal lumbar lordosis is obliterated in some, more often the sacrospinalis muscles are unduly prominent due to continuous spasm. These paravertebral muscles on one side may be more spastic resulting in mild to moderate scoliosis. Flexion, extension and lateral mobility of the trunk are limited, and commonly painful. By mild percussion one may demonstrate a well localized area of tenderness. In the supine position the pain in the back is aggravated by flexing the thigh with the leg in the extended position and this is usually more evident on one side. The tendon reflexes of the lower extremities are seldom changed and there is no alteration in the cutaneous sensibilities except in some patients there may be increased skin sensitiveness over the lower lumbar area. Early in the course of the disease roentgen-ray examination is seldom helpful. The abnormal posture of the spine may be demonstrable, an intervertebral space mildly narrowed, or in the older age group an overgrowth of bone at the vertebral margins may be observed. Narrowing of an intervertebral space as well as so-called hypertrophic arthropathy of the spine are too commonly observed in patients without pain for one to assign these as common causes for the acute disorder under consideration. Rarely, the protein content of the cerebrospinal fluid is moderately elevated and this without clinical evidence that the intradural structures are implicated. When all the available evidence is evaluated one is often forced to conclude that the patient has "pain in the lower back . . . cause unknown." There are, however, a few patients with this syndrome who have changes in the vertebrae demonstrable by roentgen-ray examination. One may arrive at an accurate conclusion regarding these and carry out appropriate definitive therapy.

For those of unknown etiology, conservative palliative measures are indicated followed by repeated observation including roentgen-ray

examinations of the involved part. The spasm of the paravertebral musculature which seems to be nature's attempt to immobilize the spine points the way for palliation. By and large, the more complete the immobilization the more effective the relief from pain. It is evident that complete immobilization is impossible in ambulatory patients. Effective limitation of movement of the trunk may be obtained by a 14 to 16 inch corset laced snugly about the lower thorax and pelvis. Other patients may be made more comfortable by a plaster of paris jacket and for still others a period of complete bed-rest is necessary. There are a few who will eventually require internal fixation by fusing the distal vertebral segments to the pelvis. It is always most important to remember that in the instances in which the causative factor for the pain has never been determined, periodic re-evaluation of the problem as if one had never seen the patient before will occasionally disclose the reason for the continued pain. Certainly surgical intervention should seldom be carried out for pain limited to the lower back unless the diagnosis is obvious and such therapy is clearly indicated.

PAIN IN THE BACK WITH RADIATING PAIN INTO ONE LOWER EXTREMITY

Not infrequently a pathological process in the lower lumbar region will result in pain limited to this area and later as a nerve root or roots become implicated the pain begins to radiate into one lower extremity. A long list of such lesions could be compiled, however, the ones commonly encountered are: fractures of vertebra, herniated intervertebral disc, spinal epidural or metastatic tumors (later involving both lowers), spinal epidural abscess, osteomyelitis, paravertebral metastatic tumor.

Of these, the outstanding examples are herniation of a part of an intervertebral disc and carcinomatous metastasis of the spinal column. Patients with the syndrome of herniated disc are more frequently encountered in office practice whereas in large municipal hospitals, carcinoma that has metastasized to the spine is an exceedingly common cause of "sciatica." The early symptoms of most patients with herniated disc are referable to the lower back. After several bouts of pain in the lower back, usually precipitated by bending or lifting and lasting from a few days to weeks, the patient begins to have pain in one buttock, along the posterolateral aspect of the thigh, in the lateral aspect of the leg and often terminating in the posterior part of the ankle. In some

the pain extends into the lateral aspect of the foot involving the fourth and little toes; in others the pain extends across the dorsum of the foot into the great toe. Pain in the back, buttocks, thigh, leg and outer side of the foot suggests a herniation of the fifth intervertebral disc whereas pain as above described radiating into the big toe suggests a herniation of a part of the fourth lumbar intervertebral disc. In addition, herniations at the fourth interspace often cause pain in the groin and this, if present, is usually experienced before the pain has extended into the lower extremity. It therefore may be said that in most instances the symptoms and abnormal physical signs that a patient should have before he is subjected to operation are: recurring attacks of pain or stiffness in the lower back with radiation of pain along the posterolateral thigh, "through" the knee into the calf or lateral aspect of the leg; numbish feeling in the lateral aspect of the leg; relative freedom from pain between attacks; moderate to marked fixation of the lumbar spine by muscle spasm; mild scoliosis (usually the lumbar spine is tilted away from the side of the lesion but under certain circumstances may be tilted toward the lesion); tenderness to percussion over the site of suspected herniation; mild diminution to absence of the ankle jerk; slight atrophy of the involved leg if symptoms are long-standing; hypalgesia of the anterolateral leg and medial dorsal part of the foot in lesions at the L₄ level; hypalgesia of the lateral leg and lateral one-third of the foot in herniations at the L₅ level. Variations of symptoms will be encountered with herniations at these common sites for the lesion (L₄ and L₅ intervertebral levels) and, as would be expected, the distribution of pain associated with the uncommon herniations at the L₁, L₂ and L₃ levels will be in accord with the spinal nerve root implicated. One should not rely on narrowing of an intervertebral disc as disclosed on plain x-ray films as an indication of the presence of a herniation at the level of the narrowing. Narrowing of the disc may be associated with dorsolateral herniation of a part of the disc; however, in the majority of instances this is not the case. Furthermore, one should not subject a patient to myelography unless there are unusual symptoms and physical signs that cannot be interpreted without the aid of this examination. A correct diagnosis is possible on clinical grounds alone in ninety per cent of patients with herniations of a part of the fourth or fifth intervertebral disc in need of surgical therapy. If there is doubt regarding the cause of the pain, be conservative. This implies relative immobilization of the

lumbar spine either by bed-rest or external appliances and the administration of analgesics for a few days to bring the acute pain under control. Paravertebral injection of a solution of novocaine will at times give some relief but the results are too uncertain for the method to be generally applicable.

Any pathological process involving a single nerve root (L_5 and S_1 in particular) may give rise to symptoms and signs comparable to those of herniated disc. The most common lesion, however, causing pain in the back and one lower extremity to be differentiated from herniated disc is metastatic carcinoma. Perineural extension of the cancer into the region of the fourth or fifth lumbar intervertebral foramen may result in symptoms simulating herniated disc. Pain due to cancer of the distal lumbar spine is usually continuous: mild, early in the course of the disease, but gradually becoming unbearable. Even the most severe pain caused by herniated disc is usually somewhat relieved by the recumbent position whereas the pain of cancer is seldom altered by change of posture. This is particularly true regarding the pain in the back. As a rule, by the time metastatic carcinoma of the spine has advanced sufficiently to cause pain in one or both lower extremities, destructive changes in the vertebral bodies are demonstrable by roentgen-ray examination. Not infrequently patients are encountered complaining of pain in the back with radiation along the anterior aspect of the thigh, numbish feeling in this area and diminution to absence of the knee jerk. As in the other syndromes, a variety of causative factors may be disclosed, however, this particular symptom-complex is most commonly the result of paravertebral metastasis or an extension into the paravertebral region of a regional malignant process. The spinal nerves are often implicated paravertebrally long before the vertebral bodies are involved. Not infrequently it is necessary to perform myelography to differentiate a lesion so placed from a neoplasm within the spinal canal.

PAIN IN THE LOWER BACK WITH RADIATING PAIN INTO BOTH LOWER EXTREMITIES

Except in examples of accidental trauma and in some instances of inflammatory lesions of the cauda equina, one seldom encounters patients who have had pain appearing simultaneously in both lower extremities. Regardless of the nature of the pathological process, those patients who eventually have pain in the back and both lower extremi-

ties usually have the initial pain limited to the back; later in the course of the disease there is pain in one thigh or leg and finally radiation of pain into both lower extremities. The following are some of the lesions that produce this syndrome: fracture of vertebra, intradural tumor, metastatic tumor of vertebra, herniated disc (occasionally), vertebral osteomyelitis (pyogenic, tbc.), postmeningitic adhesions (cauda equina).

New growths, either metastatic or primary, are the leading causes for radicular pain involving both lower extremities. Only rarely may large herniations of an intervertebral disc produce pain in both legs. The primary neoplasms are most often located in the vertebral canal, some epidural, others within the dural envelope. Those outside the dura but within the spinal canal are frequently extensions from a malignant process elsewhere, the lymphoblastomas being the most common. Those within the dura are for the most part gliomatous, arising from the filum terminale; however, a more benign tumor belonging to the meningioma group is occasionally encountered in the lumbar region. A more elaborate description of the symptoms and signs resulting from compression of the cauda equina seems inappropriate here. Suffice it to say that all patients with pain in the back and both lower extremities should be studied critically for a malignant process that has metastasized to the distal lumbar spine. In the absence of evidence of such a process in the vertebra, myelography may be indicated. Many of the primary neoplasms that grow within the dura lend themselves to total removal, however, it is seldom that those located in the epidural space can be cured by surgical therapy. The continued growth of these as well as the metastatic tumors of the vertebral bodies often produce intractable pain. Temporary respite may be obtained by intensive roentgen-ray therapy. Sooner or later it becomes necessary either to interrupt the pain-carrying pathways of the spinal cord by anterolateral cordotomy or, in some instances, to perform prefrontal leucotomy. Formerly only the spinal operation was available and this never was too satisfactory due to the fact that when performed on both sides of the cord, undesirable and troublesome disturbances in the urinary and anal sphincters ensued. Therefore this operation is being replaced by the prefrontal lobotomy. It is thought by some that appropriate division of the fiber pathways in one frontal lobe suffices, thereby obviating the intellectual blunting that may follow the operation when performed bilaterally. In our experience the one-sided procedure does not give satisfactory

results and in all the patients in whom this was carried out, the complaints of severe pain returned, necessitating the section on the other side. Recently it has been stated that the operation called topectomy now being investigated by the group at the New York Neurological Institute has been effectively employed for the control of pain. It is too soon to evaluate this procedure.

Finally, in all situations that have been listed in the three categories under consideration, surgical therapy should be employed only when the evidence available indicates a lesion amenable to such therapy. All patients with pathophysiological disturbance of unknown pathogenesis should be temporarily treated empirically but critically reviewed at intervals in an attempt to arrive at a correct diagnosis.

CLINICAL RESEARCH MEETING

Arranged by the Committee on Medical Education

JUNE 1 and 2, 1949

*An Evaluation of the Mumps Skin-Test in Pediatric Practice*ALFRED L. FLORMAN,* ALFRED E. FISCHER and
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The intradermal inoculation of killed mumps virus was introduced in 1945 by Enders, Cohen and Kane as a measure of resistance to mumps infection. The test gives a tuberculin-like reaction. Those who have had clinical or inapparent mumps previously react positively.

This test was employed during 1948-1949 in the course of a study of the epidemiology of mumps in household groups such as are seen in private pediatric practice in New York City. The antigen was formalin killed egg grown virus partially purified by centrifugation. Forty households were selected in which at least one member was ill with the disease. Skin-tests were performed on 135 individuals, 26 of whom were first cases and 109 of whom were contacts. Among the contacts there were 80 adults and 29 children.

The reactions, especially among the children, were often difficult to read. The ery-

thema was sometimes faint and its edges poorly differentiated. All of the first cases gave negative reactions during acute illness. When 6 were retested several months later 5 had become clearly positive and one questionably so. Among the contacts there were 60 positive and 49 negative skin-tests. Only one half of the positive reactors definitely recalled having had the disease.

Within the following 3 weeks, 12 of the contacts became ill with clinical mumps. Only one of these contact cases was among the positive reactors and 11 were among those with negative skin-tests. Since the 49 negative reactors consisted of 22 adults and 27 children, it is significant that 10 of the secondary cases occurred among the children.

It is concluded that although the test is useful in determining susceptibility to mumps, a positive skin reaction is not the sole indicator of resistance.

* Aided by a grant from the Sara Welt Foundation.

Hypermetabolism Without Hyperthyroidism

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It is an accepted fact that there are clinical conditions in which the basal metabolic rate is elevated in spite of the fact that none of the features of hyperthyroidism

is present. Clinicians have known for a long time that many of the patients suffering from hypertension, polycythemia, leukemia, malignant lymphomas, generalized or local-

ized malignant growths, Paget's disease of the bones, and other diseases frequently present an elevation of the basal metabolic rate. It is also well recognized that these patients do not present the classical signs of hyperthyroidism and the pathological changes in the thyroid gland do not suggest the typical hyperplasia and other alterations of Graves' disease.

We have attempted to study thyroid function in this group of patients with elevated basal metabolic rates by determining the level of the non-dialyzable (protein-bound) blood iodine and the urinary excretion of tracer doses of I 131.

Both of these methods show constant changes in hyperthyroidism. In this disease the "hormone" iodine is consistently elevated in the blood and the urinary excretion of tracer doses of I 131 is reduced due to the

increased avidity of the thyroid gland for iodine.

In a series of over 100 consecutive patients suffering from the diseases outlined above whose metabolic rates were elevated and who presented no clinical signs of Graves' disease, we determined the blood iodine levels in all and the I 131 excretion in some. Without exception, the blood iodine levels and I 131 excretion were normal in spite of very marked elevations of the basal metabolic rate.

Summary: In hypermetabolic states not due to hyperthyroidism, the function of the thyroid gland is normal as measured by the level of the protein-bound blood iodine and the urinary excretion of I 131. The increased metabolism in these disorders is apparently not mediated through the thyroid gland.

The Association of Interatrial Septal Defect and Anomalies of the Osseous System

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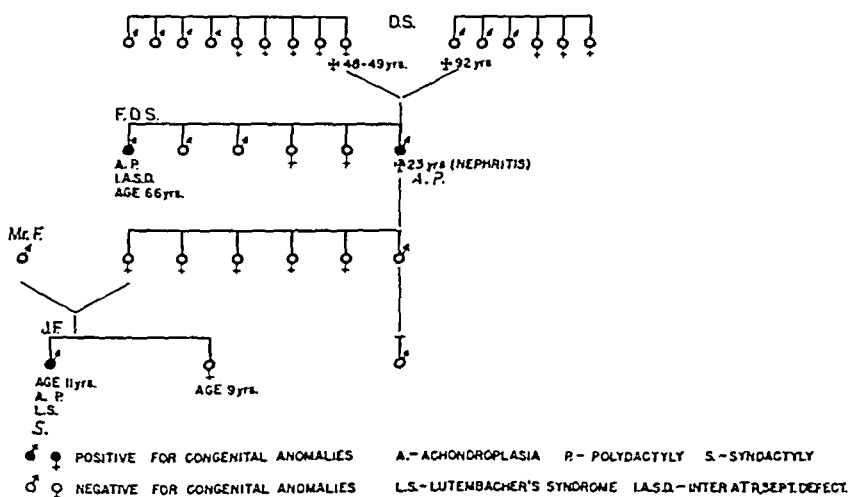
The association of congenital defects of the heart with those of the locomotor system is relatively rare. Arachnodactyly has been reported in combination with interatrial septal defect and with congenital aneurysm of the aorta. Achondroplasia in association with patent ductus arteriosus has been mentioned once in the literature. We have observed several cases of congenital cardiac defects in patients with rare anomalies of the osseous system. The congenital cardiac anomaly encountered was invariably an interatrial septal defect either alone or in association with a congenital mitral stenosis. Five illustrative examples of the association of such a congenital cardiac anomaly with various abnormalities of the osseous system are herewith reported.

In the first 2 patients (grandfather and grandson) the family history is of particular interest, as depicted in the accompanying

genealogical chart. The grandfather (case 1) is an achondroplastic dwarf, with polydactyly of the hands, interatrial septal defect, hypertension, coronary artery disease and congestive heart failure.

The grandson (case 2) now an 11-year boy presents the following congenital defects: achondroplasia, polydactyly, syndactyly and interatrial septal defect with congenital mitral stenosis (Lutembacher's syndrome).

In the third case, no congenital stigmata are known to exist in the family. He is a 12-year old boy. His bony deformities consist of congenital synostosis of several cervical vertebrae (Klippel-Feil syndrome), bilateral multiple anomalies of the carpal bones, cervical ribs and subluxation of the right thumb. His cardiac anomaly is an interatrial septal defect.



Patient 4 is a 21-year old male whose parents are first cousins, but free of congenital anomalies. The patient has polydactyly and so has his sister, her only daughter, and his first cousin's daughter. None of the members of his family have heart disease. The patient himself is only 4 feet 9½ inches tall, weighs 90¾ lbs. and is of proportionate build, with almost no pubic, facial or axillary hair. Polydactylism and webbing of the second and third toes of both feet are present. His cardiac anomaly is Lutembacher's syndrome. He is a hypophyseal dwarf.

The fifth patient, a 6-year old girl, was the first member of her family to be afflicted

with multiple congenital anomalies. She has polyphalangism of both thumbs associated with bilateral absence of opponens action of these digits. The cardiac lesion was a Lutembacher's syndrome.

We find that the congenital cardiac lesion when associated with congenital bony defect is usually an interatrial septal defect, with or without congenital mitral stenosis. The familial occurrence of the osseous anomalies in 3 patients indicates that the cause can hardly be ascribed to an intra-uterine fault. The presence of an interatrial septal defect in all of the 5 cases suggests that the lesion is rather of genetic than of intra-uterine origin.

Simultaneous Left and Right-Sided Intracardiac Electrocardiography in Man: Right Bundle Branch Block

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Catheterization of the right cardiac chambers and pulmonary artery has been widely applied to the study of cardiac dynamics and for the analyses of right sided intracardiac potentials. Retrograde catheterization of the aorta from the femoral, brachial, or axillary artery has been employed for

direct aortography. As yet, retrograde left cavity catheterization for the study of hemodynamics or cavity potentials in humans has not been reported. During our intensive study of cavity surface, esophageal, chest and extremity potentials in man, we thought that the simultaneous recording of

right and left sided cavity potentials would be important. Patients with right bundle branch block permit particularly well the analyses of the initial ventricular deflection in the left ventricular cavity without interference from right ventricular activity.

The retrograde catheterizations of the left ventricle were carried out from either common carotid artery. The radio-opaque catheter was either a No. 3.5 French fitting through a No. 16 gauge needle or a No. 5.0 French fitting through a No. 13 gauge needle. With direct surgical exposure as done for cerebral arteriography, the needle with the catheter was inserted into the common carotid artery and directed against the blood stream towards the aortic valve. The catheter was positioned under fluoroscopic control with the needle remaining in the carotid artery. There is less trauma to the arterial wall if the needle remains in position and serves as a sleeve for the catheter. Retrograde passage through the aortic valve was very difficult because of the high forward pressure. It was best accomplished by allowing the catheter to form a coil. The catheter for recording the right cavity potentials was introduced into an antecubital vein of either arm. Spot films were taken whenever electrocardiograms were recorded.

Because this study was of investigative nature, patients with advanced metastatic malignancy were chosen as subjects.

The electrocardiogram in the case of the right bundle branch block to be demonstrated shows the following:

Left ventricular cavity: deep QS pattern with a terminal second QS shaped wave and positive T-wave. The stimulus traversing the septum from left to right reaches the right ventricular cavity in 0.025 sec.

Right ventricular cavity: the initial R-wave reaches its peak in 0.02 sec. and the second R wave in 0.08 sec., evidence of marked delay of right ventricular stimulation. The T wave is inverted.

These findings are identical with those obtained by Wilson et al. in animals. In normal individuals, right ventricular cavity leads often but not invariably show an initial R-wave. In this case of right bundle branch block the left ventricular cavity lead shows a QS wave. It therefore appears that in humans as in canines the stimulus to the ventricles reaches the left portion of the septum first and only then spreads to the right side.

Studies are in progress to supplement these studies with left ventricular catheterizations via the pulmonic veins which are exposed during pneumonectomies.

*Anomalous Atrio-ventricular Excitation Produced By Catheterization of the Normal Human Heart**

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In the course of a comprehensive study of the intracardiac potentials developed during electrical activity of the human heart we have on two occasions, while manipulating the catheter, seen what appeared to be anomalous atrioventricular excitation (pre-excitation) in normal subjects. In both instances the abnormal rhythm occurred while the catheter was being moved in the

heart or just after movement had ceased. On one occasion there was some aberration of the ventricular complex in the intracardiac record which was not reflected at all in the simultaneously recorded external lead. On other occasions, ordinary premature systoles of ventricular origin occurred.

The data may be interpreted in one of three ways: 1) the catheter increased the

rhythmicity of a center in the ventricular muscle which then fortuitously discharged at a rate similar to, but preceding, impulses from the sinoatrial node; 2) the catheter itself, extending as it does through the right atrium, was moved by contraction of this chamber to a sufficient degree to make more distal parts of it in the ventricle stimulate the latter prematurely, probably in the region of the upper right side of the interventricular septum; 3) the catheter increased the irritability of a ventricular center which was then discharged prematurely by atrial systole, either electrical or mechanical.

By indirect reasoning, the third interpretation is believed to be correct.

In the past, two mechanisms have been advanced to explain the spontaneous occurrence of the type of electrocardiogram under discussion. One of these is anatomical,

the other physiological. The former ascribes anomalous atrioventricular excitation to the existence of one of several anomalous pathways of conduction between the atria and the ventricles. A fallacy of the anatomical concept has been to ascribe a function of conduction to a tract simply because it has been found to exist at necropsy in a patient known to have shown the abnormal electrocardiogram during life. Adequate attention does not seem to have been paid to control observations; it is not known what number of subjects will display such tracts at necropsy who never had the abnormal electrocardiogram during life.

The data presented do not disprove the anatomical concept but do revive interest in a possible physiological approach to a final understanding of the exact mechanism in anomalous atrioventricular excitation.

Ergotamine Tartrate and the "2-Step" Exercise Electrocardiogram in Functional Heart Disturbance and in Organic Heart Disease

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and ARTHUR M. MASTER

Patients with severe neurotic complaints, including chest pain, may exhibit pronounced RS-T depressions and T-wave inversions in the "2-step" exercise electrocardiogram and in the 10 per cent oxygen test, indistinguishable from those found in organic heart disease. Because of the obvious clinical implications stemming from these facts, we have attempted to elucidate the mechanism of the electrocardiographic aberrations in psychoneurotic subjects following the "2-step" exercise test and to offer a means for the differential diagnosis of organic and functional heart disturbance.

The "2-step" exercise tolerance test was performed in ten patients with signs and symptoms referable to the heart before and after the intravenous administration of ergotamine tartrate. In the five cases which were classified as functional the "2-step" exercise test was positive before ergotamine

but negative after its administration. In the five cases known to be affected with organic coronary artery disease the "2-step" test was positive both before and after the ergotamine injection. In other words, in the patients with functional heart disturbance there was consistent prevention of electrocardiographic abnormalities following exercise by ergotamine, whereas in patients with organic coronary artery disease the administration of ergotamine did not alter the abnormalities which appeared after exercise.

Ergotamine was administered intravenously in $\frac{1}{3}$ to $\frac{1}{2}$ mg. doses. The effects became marked in 15 to 30 minutes and lasted one hour or more. A drop in pulse rate of 20 to 30 beats per minute was common along with a rise in blood pressure of 20 to 40 mm. of mercury. Elevation of T-waves was observed.

The exact mechanism of alteration of the RS-T segments and T-waves of patients with functional disorder is unresolved. Lability of the autonomic nervous system, diminution in coronary blood flow or direct nervous effects on cardiac metabolism have been suggested.

It has been accepted that ergotamine is adrenolytic and sympatholytic in the doses employed in experimental animals, usually of the order of 0.05 to 0.1 mg/kilo body weight. There is no definite evidence that in the dosages employed clinically in man (0.5 mg.) it possesses similar properties. The complicated effects of ergotamine tartrate on the heart, including its poorly understood nervous system effects, and the vasoconstrictive action on the coronary vessels preclude any simple explanation of its effects on the electrocardiogram of neurotic

patients. Despite the theoretic uncertainties touched upon above, its effects are quite definite in the prevention of abnormalities in the electrocardiogram of patients with functional heart disorders.

The side reactions to ergotamine tartrate given intravenously were nausea, vomiting, and in two of the patients with coronary artery disease, attacks of angina pectoris. The routine clinical use of ergotamine is contraindicated in such cases because of its anginal provoking properties.

Further studies on the relationship of the vegetative nervous system and the electrocardiogram with the newer autonomic drugs may elucidate some of the problems raised by this study and provide accurate clinical methods for distinguishing functional from organic heart disease.

*Effect of An Adrenolytic Compound, Dihydroergocornine, on Epinephrine-Induced Stimulation of the Adrenal Cortex**

STANLEY AUGUST and RICHARD GUBNER

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Epinephrine has been shown by Vogt to be a physiological stimulus to the production of adrenal cortical hormone, presumably mediated via the adrenocorticotrophic hormone of the anterior pituitary (Long). Because of the possible bearing of this mechanism on the adaptation syndrome of Selye, and also on the question of neurohormonal interrelationships in hypertension it was thought of interest to investigate whether the stimulation of the adrenal cortex by epinephrine could be inhibited by adrenolytic compounds. Dihydroergocornine has been shown to possess potent adrenolytic and sympathicolytic actions, i.e., inhibition of excitatory epinephrine effect on rabbit uterus, inhibition of epinephrine induced hyperglycemia, inhibition of relaxing effect of epinephrine on intestine (Rothlin), diminution of pressor response, tachycardia and mydriasis following epinephrine (Freis,

Stanton and Wilkins).

As an index of adrenal cortical stimulation the fall in eosinophiles and lymphocytes produced by epinephrine was studied, employing the Laragh modification of the test described by Thorn and co-workers. Following control eosinophile and lymphocyte counts 0.5 mgm. of epinephrine was given subcutaneously to eight subjects, twenty minutes after intravenous injection of 0.5 mgm. of dihydroergocornine. The response was compared with control administration of epinephrine alone two to four days later. Following epinephrine alone an average reduction in eosinophiles of 54.6 per cent from an initial count of 194/mm³ occurred, whereas when epinephrine was given following dihydroergocornine the average decrease in eosinophiles was 56.5 per cent from an initial count of 201/mm³. Reduction in the lymphocyte count following epinephrine

alone was 29 per cent; following epinephrine and dihydroergocornine an average fall of 53 per cent occurred. Control lymphocyte counts were found to be more variable than eosinophile counts, and the eosinophile response in accordance with the experience of others is considered a more dependable index of adrenal cortical stimulation.

The findings demonstrate that dihydroergocornine does not produce any significant inhibition of epinephrine stimulation of the

adrenal cortex. That dihydroergocornine otherwise exerted adrenolytic and sympatholytic activity in these experiments was indicated by reduction in blood pressure, modification of response to the cold pressor test and inhibition of epinephrine hyperglycemia. The combined use of dihydroergocornine with epinephrine or epinephrine-in-oil provides a method for therapeutic stimulation of the adrenal cortex, avoiding the undesirable side effects of epinephrine.

Autoantibodies in Different Phases of Human Glomerulonephritis

KURT LANGE, DAVID WEINER, MICHAEL M. A. GOLD,
VICTOR TCHERTKOFF and VERA SIMON

The clinical facts which lead to the hypothesis that human glomerulonephritis is an organ specific antigen-antibody reaction will be reviewed together with the experimental evidence gained by heterologous antikidney serum injections. Using a further modification of Cannon and Marshall's collodion technique and its later modification by Cavelti, the authors have examined the sera of 51 nephritics of all stages and of 126 controls for the presence of antibodies to human kidney.

It was found that in 72.7 per cent of the tests done in cases of all stages of glomerulonephritis high positive titres can be obtained (average 1:412). The percentage of positive cases and the titres are higher in the later stages of glomerulonephritis than in the first month of the disease.

Twenty-eight determinations were done on 12 cases during the first month of the disease yielding an average titre of 1:107 with only 42 per cent of the cases being positive more than 60 per cent of the time.

Two hundred and twenty-one determinations were done in 39 cases after the first month of the disease yielding an average titre of 1:450 with 79.5 per cent of the cases being positive more than 60 per cent of the time. This difference may largely be due to the fact that during the first few

days of acute glomerulonephritis no antibodies can be found in the serum since they are completely absorbed in the kidney.

Two hundred and five determinations performed on 126 normal controls yielded an average titre of 1:46 with only 17.5 per cent of the cases positive 50 per cent of the time or more.

Renal antigens obtained from infants or still-births show a much greater specificity and higher titres than antigens from adult renal tissue, a fact which may explain the high incidence of glomerulonephritis in young individuals.

The continuous presence of antibodies to kidney throughout all stages of the disease except the first few days forces one to assume that human nephritis does not result from a single insult with subsequent scarring but rather from the constant presence and occasional stimulation of antibodies to renal tissue.

Neutralizing these antikidney antibodies by means of kidney tissue emulsions or extracts should be carefully investigated as a possible therapeutic approach.

The use of antihistaminic drugs to mitigate the vascular effects of such an antigen-antibody reaction should also be investigated further.

After an average follow-up period of 18 months, interim evaluation of results is as follows:

Effect on Ulcer Symptoms

Excellent (Symptom free).....	18%
Good (Symptoms improved).....	36%
Fair (Temporary or incomplete relief)	12%
Failure	34%
Early from atony.....	10%
Late, full recurrence.....	24%

Nine (18%) of the failures required further surgery from three weeks to twenty-seven months after vagotomy. Seven had gastric resection and two had gastroenterostomy performed. Three of these cases subsequently developed marginal ulcers despite apparently complete vagotomy.

Effect on Ulcer as Demonstrated by X-ray

Active Ulcer—

Niche and/or deformity, irritability, spasm, and tenderness..... 38%

Inactive ulcer—

Deformity alone..... 42%

Early failure

No X-rays after three months..... 8%

Unknown

Secondary prolonged disturbances in gastric motility were observed on X-ray examination as follows:

Unremitting atony requiring early

surgical intervention..... 10%

Prolonged atony

>100% enlargement

>50%—6 hr. retention..... 6%

Moderate atony

>30% <100% enlargement

<50%—6 hr. retention..... 30%

Slight atony

<30% enlargement

No retention..... 6%

Normal stomach

No change observed..... 36%

Unknown

According to the authors' data, a patient who is subjected to vagotomy has one chance in five of securing complete relief, two chances in three of being benefited to some extent, and one chance in three of failure, all within an average of eighteen months postoperatively. For this rather dubious benefit he must accept a small but nevertheless significant mortality risk and the unhappy prospect that his continued freedom from ulcer symptoms is by no means assured. Half the time he must also pay an additional premium in the form of persistent symptoms of gastric atony which not infrequently may be more disabling than the original ulcer.

On the whole, the authors feel that vagotomy, even in carefully selected cases, has not proven successful in a sufficient number of cases to justify its routine use. Despite the lower operative mortality, failures are too frequent and morbidity too serious after vagotomy to justify its replacement of other more effective methods of surgical treatment.

A Method for the Preparation of Exteriorized Skin Covered Loops of Intestine for the Study of Bowel Obstruction

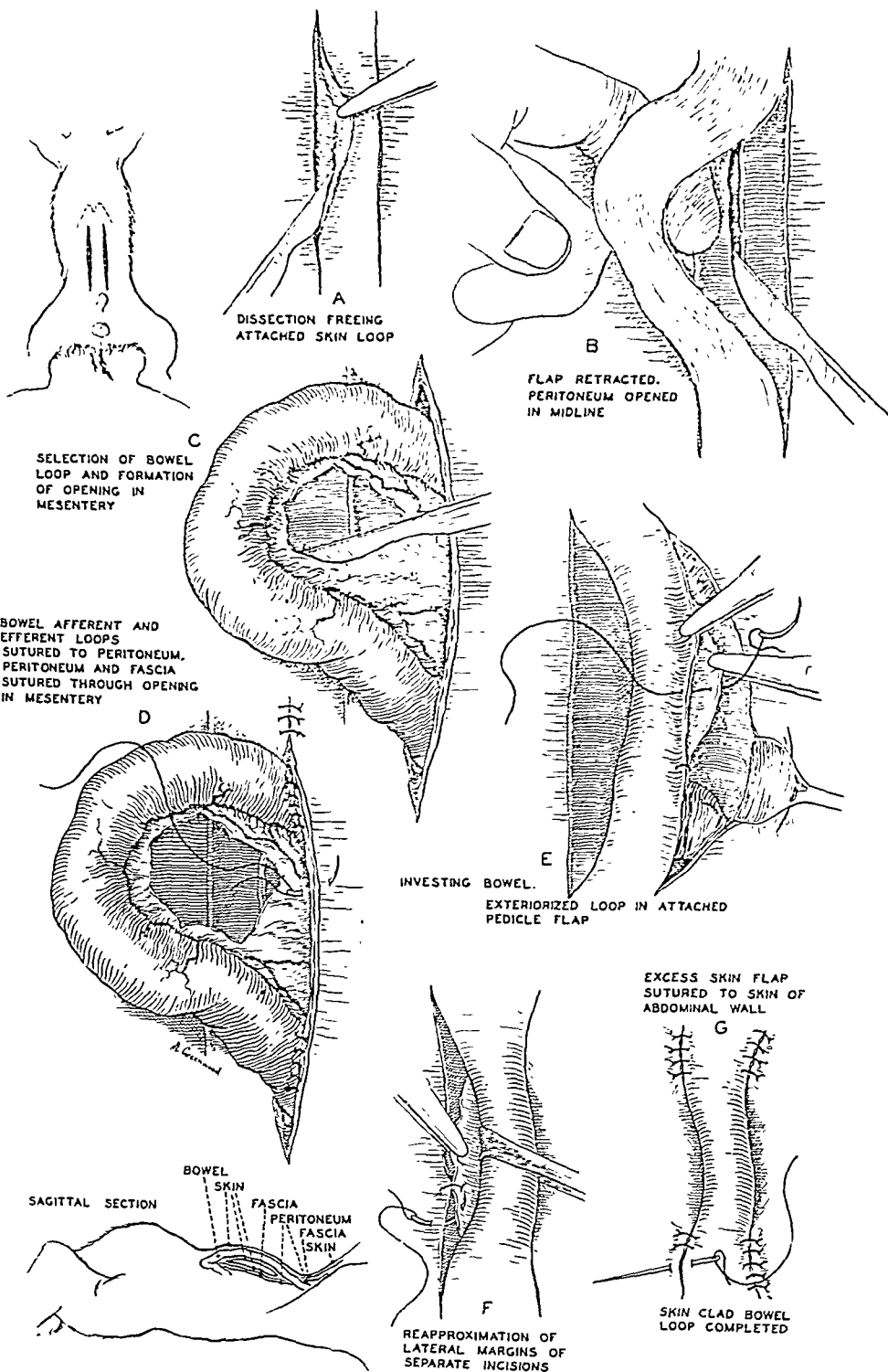
ROBERT T. CROWLEY and DONALD A. DAVIS

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In the course of certain experiments concerned with intestinal obstruction it is advantageous to prepare exteriorized loops of intestine which can be obstructed for varying periods of time and then released without the necessity of repeated operations. The following preparation can serve such

purpose in that the animal can be kept in a normal state for long periods of time and may be used for study at will. There is no exposure of naked loops of intestine and the continuity of the gut or its nerve or blood supply is not interfered with.

Two straight incisions placed $2\frac{1}{2}$ inches



on either side of the midline are made. These incisions extend down through the skin and subcutaneous fascia, permitting a layer of skin to be raised which is attached at the upper and lower ends. The abdomen is opened through a midline incision beneath the segment of skin. The loop of bowel to be exteriorized is then brought out and the peritoneum, muscle, and fascia closed about the loop of intestine through its mesentery. It is necessary to suture the peritoneum through an opening in the mesentery made in the area where there are no vessels or nerves. The approximation of the peritoneum, muscle, and fascia must be brought loosely about the vessels so as not to cause constriction. The flap of skin which has been raised from the midline as a pedicle graft is then approximated about the loop through the aperture in the mesentery. A free space is left which traverses the mesentery and the skin in this area so as to permit the application of a clamp or other means of obstructing the bowel. The skin on either side of the midline incision is then undercut sufficiently to allow approximation to the

edges of the skin which also pass through the aperture in the mesentery together with the peritoneum and fascia.

It can readily be seen from the diagram which is presented (see figure) that this preparation permits of sampling from the intestine by the insertion of a needle through the skin and gut which lies beneath it. If such sampling is carried out, the needle ought to be extended tangentially for a distance through the skin and the loop in order that intraenteric pressure will tend to close the needle hole without leakage.

When it is decided to produce a simple obstruction, all that is necessary is to apply a clamp at one end of the loop. If a closed loop obstruction is desired, a clamp may be placed on both ends of the loop.

Studies to determine the relation of the autonomic nervous system to intestinal obstruction are being undertaken. This preparation lends itself readily to experiments and because of its simplicity it may be of considerable use to others who are carrying on similar studies.

*The Biological Chemistry of Wound Healing: Effect of Blocking the Sulfhydryl Group (-SH) in Vivo with Iodoacetic Acid**

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Previous studies have shown that protein depletion impedes the rate of healing of laparotomy and of surface wounds in rats. It has also been shown that dl-methionine administered parenterally following infliction of the wound serves to return the curve of wound healing toward normal. The cause and nature of this effect of methionine has been sought. Possible hypotheses include the following: 1) Liver function may be improved by the lipotropic effect of the methionine. 2) The healing wound may require the specific amino acid methionine as a raw material in a quantity beyond that available to it by catabolism of its own

tissues in the protein-depleted state. 3) Since the skin and connective-tissue are relatively rich in organic sulfur, the sulfhydryl portion of the methionine molecule may be essential to the normally healing wound.

The last hypothesis has been tested by chemically blocking the —SH radical with parenterally administered iodoacetic acid. This compound has been shown to inhibit the sulfhydryl group of various enzymes and other compounds in vitro and in vivo. It also inhibits growth in normal young rats.

A series of albino rats received iodoacetic acid for a total of 10 days immediately pre-

ceding and following infliction of a standard laparotomy wound. Groups of animals were killed on the 3rd, 4th, 5th, and 6th days postoperatively, and the tensile strength of the wounds was tested. A significant lowering of the tensile strength was noted when compared with normal rats.

A third group of rats was tested which were in every way identical with the first group except that in addition to iodoacetic acid they were given an excess of di-

methionine, a physiological precursor of sulphydryl-containing compounds. These rats showed acceleration of healing when compared with the iodoacetic acid-treated rats.

It is concluded that blocking the $-SH$ radical in vivo impedes wound healing in otherwise normal rats. The possible site of this blocking effect is briefly discussed as is its significance to the wound-healing problem.

Starch Sponge—A Hemostatic Agent

SAMUEL S. ROSENFELD

A number of highly efficient blood coagulants have recently been introduced into medical practice and have been found of great value. The reasons that impelled the author to describe yet another hemostatic agent is its demonstrated effectiveness and low cost.

In 1947 a patent was granted the U. S. Department of Agriculture for the manufacture of an absorbable starch sponge. The dry sponge is capable of absorbing sixteen times its weight of water, and the department was interested in it because it could absorb appreciable amounts of medicaments such as penicillin, gramicidin, sulfapyridine, etc. and is slowly absorbed from body cavities.

It seemed to the author that the chemical and physical nature of the starch sponge made it highly probable that it also possessed blood coagulating properties.

Numerous experiments have demonstrated that the starch is taken up by the peritoneum and is metabolized like any ingested starch. No sensitizing or anaphylactogenic properties were encountered. The majority of investigators state that the tissue reaction to starch is not significant. Our own experiments confirm this statement. We left large pieces of dry and wet sponge amongst coils of the intestine without opening any large vessel. At autopsy gross inspection in the majority of these animals revealed none or negligible adhesions.

Taking into consideration the fact that the vena cava is located in the retroperitoneal space, the cellular tissue of which is almost embryonal in its reaction to stimuli, the adhesions we found at autopsy (usually three to four weeks after operation) were surprisingly moderate.

The blood coagulating properties were demonstrated by us on rabbits, using suitable controls. We employed the large veins of the ear, the femoral vein, and the inferior vena cava.

In every case where the starch was properly applied to any of the above-mentioned incised vessels, including the vena cava, the animal survived. All controls died when the larger vessels were opened.

To date, we have used the starch clinically 76 times to control bleeding. In 35 instances, the bleeding was intraperitoneal; in 29 cases, it was vaginal; in 10 patients cervical and in 2 rectal. The procedures in which these applications were made included: abdominal and vaginal hysterectomy, myomectomy, ruptured corpus luteum cyst, and cesarean section. In some of the cesarean cases the starch was introduced into the uterine cavity through the uterine incision.

The starch added greatly to the safety of the operation, especially in hysterectomy where the oozing was easily controlled, thus obviating clamping and possible ureteral injury.

There was no mortality in this series.

There was no morbidity that could actually be attributed to the starch.

Starch sponge is an efficient hemostatic agent. Its effects appear to be purely local and its hemostatic action is probably due to its gel formation, which permits it to absorb many times its weight in blood. This

property causes the sponge to swell and exert pressure on the bleeding points. An additional barrier to blood loss is its adhesive quality.

An important factor is its low cost. It can be produced for as little as 7 cents a pound.

Management of Ascites Due to Cirrhosis of the Liver; the Use of "Rice" Diet, Blood and Plasma, Diuretics and Surgery

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JERE W. LORD, JR.

From New York University Post-Graduate Medical School and Fourth Medical
and Surgical Divisions of Bellevue Hospital

Kempner has demonstrated that hypertensive patients maintain protein balance on the rice-fruit-sugar diet which contains approximately 470 gms. of carbohydrate, 20 gms. of protein and 5 gms. of fat per 2,000 calories. Further, this diet is low in salt, having less than 150 mgms. of sodium and 200 mgms. of chloride.

It occurred to us that the cirrhotic patient with ascites might obtain benefit from the "rice" diet by virtue of its low salt composition, particularly when a protein hydrolysate low in sodium and high in tryptophane (120 gms. of powder contain the equivalent of 70 gms. of protein) was added daily. The sodium content of the powder is less than 50 mgms. per 100 gms. In addition, anemia and hypoproteinemia were treated with transfusions of whole blood or plasma and daily vitamin supplements were supplied. In several patients diuresis was achieved only by the use of intramuscular mercurhydrin given concurrently with blood or plasma infusion.

Six patients suffering from intractable ascites due to cirrhosis of the liver have been managed by the "rice" diet and the early results to date have been encouraging. One patient, a 36 year old white man, entered the Fourth Medical Division of Bellevue Hospital on October 4, 1948, complaining of ascites of 2 months duration, abdominal pain, anorexia and weakness. A

diagnosis of cirrhosis of the liver of alcoholic-nutritional etiology was established and the usual high protein high carbohydrate, low fat, low salt diet was instituted. Anorexia, ascites requiring paracentesis, and weakness persisted. Of poor prognostic significance from past experience, were the anemia, a large smooth liver and the febrile course. The patient's course was slowly downhill, in spite of the use of diuretics and the "Patek regime" until November 18, 1948 when the rice-fruit-sugar diet, with the addition of the oral protein supplement was instituted. During the next 7 weeks the patient lost 33 pounds in weight, his abdominal circumference decreased from 100 cms. to 72 cms. and his appetite and strength improved. Prior to the institution of the "rice" diet, the patient had had a massive gastrointestinal hemorrhage requiring 3 transfusions. A gastrointestinal roentgen series failed to reveal esophageal varices or a peptic ulcer. The patient has been free from ascites for 3 months and in good condition with the exception of a small residual left hydrothorax which shows no evidence of a neoplastic or tuberculous etiology. A high red count and hemoglobin and normal blood protein fractions have been sustained.

Of the remaining 5 patients, one was showing marked improvement on the regime but succumbed to a massive gastrointestinal

hemorrhage during the second month of therapy. Three others have not required paracenteses while on the diet over periods of 4, 3 and 2 months respectively. The sixth patient is a 43 year old man with portal cirrhosis on an alcoholic nutritional basis who required approximately 40 taps over a period of 10 months. During one month of the regime no paracenteses were required, although some ascites persisted. Because an esophagram showed esophageal varices, the patient was subjected to a portacaval shunt (an end-to-end anastomosis of the portal vein with inferior vena cava, through a right sided thoraco-abdominal approach) with a lowering of the portal

pressure of 475 to 190 mms. of water when the shunt was opened. His post-operative course was smooth except for 3 or 4 days of intermittent mental confusion.

In summary, the "rice" diet supplemented by certain important factors such as added oral salt-free protein, vitamins, concurrent use of plasma and blood transfusions with mercurial diuretics proved to be an effective form of therapy in the management of intractable ascites due to cirrhosis of the liver. In one instance the above regime proved to be excellent for the pre-operative preparation of a patient subjected to a portacaval shunt.

Carbohydrate Utilization in Surgical Patients: The Blood Lactic Acid in Pre- and Post-Operative Patients After the Administration of Glucose

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Abridgement of thesis submitted to the Faculty of the Graduate School of the New York Medical College in partial fulfillment of the requirement for the degree of Master of Medical Science in Surgery

During the post-operative period glucose is the chief source of nutrition. It is, therefore, essential to determine whether the glucose given is actually utilized or simply stored. Many studies on this subject indicate that the coefficient of correlation for grams of glucose given and grams retained is high. Unless the sugar is burned, however, post-operative starvation ketosis and hypoproteinemia will occur.

That glucose is capable of immediate oxidation following absorption is a general assumption. Koster, however, in 1930 used the respiratory quotient as the index of carbohydrate combustion and found that a normal rise in the respiratory quotient following the intravenous injection of glucose did not occur until the fifth post-operative day. He concluded that a carbohydrate metabolic disturbance existed during this period. His work has never been duplicated or challenged.

The psychic and organic effects of major surgery can cause marked alterations in the

bodily metabolic processes. The classical demonstrations of Cannon indicate the psychic effects upon the adrenals and Selye and others have shown the influence of trauma, blood loss and shock on the carbohydrate metabolizing hormones.

The use of the respiratory quotient as a criterion of carbohydrate utilization has been violently attacked by Soskin and Levine. The use of the blood lactic acid response to glucose as an indicator has gained general recognition. Root and Carpenter in 1946 checked their previous observations concerning the ability of the diabetic to burn sugar using the blood lactic acid.

In order, therefore, to determine whether the post-operative period is characterized by inadequate sugar metabolism, it was decided to utilize the lactic acid of the blood as an indicator.

Method: Ten patients were studied in the pre- and post-operative periods. Pre-operative results were used as the norm. All patients were given high doses of vitamins

daily before study. Patients who were febrile or who showed kidney or liver damage were excluded. Young and old patients of both sexes in good, fair and poor general condition were included. The operative procedures varied widely in type and duration. The amount of each anesthetic agent administered was estimated.

A 300 cc. aqueous solution containing 50 gms. of glucose was given intravenously during an interval of twenty minutes. All patients were in the post-absorptive state. The blood lactic acid and blood sugar as well as the cephalin flocculation and thymol turbidity were determined from a sample of blood withdrawn just before the infusion of glucose. These served as the base-line values. Blood was withdrawn every thirty minutes for two hours thereafter for lactic acid and sugar determinations. The total amount of sugar excreted in the urine was determined quantitatively. The fluid intake and output were carefully recorded.

Results: There was an increase in the blood lactic acid in all patients in both the pre- and post-operative periods following the intravenous administration of glucose. The average rise noted during both periods was of approximately the same magnitude. The rise also corresponds with that observed in normal subjects by other investigators. Experiments were carried out for from two to 17 hours post-operatively. The

maximum rise in lactic acid did not occur regularly within a constant period after glucose administration. This confirms the observations of others that the lactic acid cannot be correlated quantitatively with the blood sugar curve. The rise does indicate, however, that glucose was definitely in the process of oxidation in all patients during the post-operative period.

Blood sugar levels post-operatively were slightly higher than the pre-operative values. Approximately three times as much sugar was lost in the urine of patients post-operatively. Fluid balance data did not show that hypertonic glucose solutions cause excessive fluid loss post-operatively. This observation has also been made by other investigators.

CONCLUSIONS

1. Lactic acid, an intermediary compound in carbohydrate metabolism, has been studied in pre- and post-operative patients following the intravenous administration of glucose.

2. The blood lactic acid increase observed in all patients demonstrates that glucose is capable of oxidation and utilization in the pre- and post-operative periods.

3. Glucose was not found to be associated with excessive glycosuria or fluid imbalance when administered intravenously in the immediate post-operative state.

Studies with the Quantitative Cephalin-Cholesterol Flocculation Reaction

Effect of variation in temperature at which Hanger reaction occurs.

The protein patterns of normal and abnormal liver-disease sera

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In a previous publication (J. Clin. Invest. 37, 737 (1948)) a method was described for determining small variations in the cephalin-cholesterol flocculation reaction (Hanger) by means of *quantitative* cholesterol determinations. The results are expressed as cholesterol units. By means of this pro-

cedure the effect of temperature on a large number of normal and abnormal sera were studied. A marked variation was found in the amount of flocculation obtained with the same serum at different temperatures.

These temperature studies indicate that all human sera with suspected liver disease

can be divided into four serum protein patterns based on the cholesterol unit values obtained at 4°, 25°, 37.5° and 56° C. These patterns are classified on the basis of severity of liver damage as follows:—

- Type I: Normal sera
- Type II: Slight liver damage e.g. chronic hepatitis
- Type III: Moderate liver damage e.g. acute hepatitis
- Type IV: Severe liver damage e.g. cirrhosis

Serial studies on a single case of acute infectious hepatitis from the peak of the attack to date of discharge, show a gradual

change in the pattern from Type IV to Type I as the clinical condition of the patient improved.

Cases of infectious mononucleosis or malaria, which are often associated with liver damage, exhibit the same serum protein patterns as do cases of infectious hepatitis. Similar liver disease patterns were found in some cases of multiple sclerosis.

These changes in the serum protein patterns obtained with this simple technique in various liver disease cases parallel those found by other investigators employing the more elaborate electrophoretic procedures.

Hemophilioid Disease

A hemorrhagic disease with prolonged coagulation time and a circulating anticoagulant. Report of a case in a female

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In 1940 Lozner, Jolliffe and Taylor were the first to recognize a hemophilia-like disease associated with a circulating anticoagulant. There have been a total of ten reported cases; of these, two were in women. The present study is concerned with a young woman who manifests this disease.

F. L., a thirty year old white female with no past or familial bleeding history, had an uneventful second delivery in November 1947. Seven weeks later she had a mild siege of pains in the thigh and the popliteal region, slight fever, and leukocytosis. Three months post-partum she developed a large hematoma in her right jaw following a dental procedure. In March 1948 ecchymoses and pain in the left leg appeared. This was accompanied by a prolonged coagulation time of 39½ minutes (normal 6-12) of the venous blood. The blood picture was otherwise unremarkable; likewise the platelets, prothrombin, tourniquet test, bleeding time, clot retraction, calcium, and fibrinogen were all normal. In July 1948 renal colic and hematuria occurred. The hematuria did not respond to transfusions, so that the patient

had to be hospitalized during August 1948. Anti-hemophilic globulin, protamine, and fresh blood serum, as well as whole fresh blood, were administered but these had no effect upon the hematuria or the prolonged clotting of the blood.

Special studies were made to determine the underlying cause of the abnormal clotting:

1. The patient's blood was mixed with normal blood and was found to prolong the coagulation of the normal blood. This indicated the presence of anticoagulant in her blood.

2. The anticoagulant factor was present in plasma and serum as well as in whole blood.

3. Ammonium sulfate fractionation of the plasma indicated its presence in the pseudo-globulin fraction.

4. It was thermostable at 56° C.

5. It was not dialyzable.

6. The electrophoretic curve of the plasma was normal.

7. The anticoagulant was not neutralized by protamine, toluidine blue, or anti-

hemophilic globulin.

8. There was no increase of anti-thrombin.

9. Conversion of prothrombin was not delayed.

10. Factor VI of Owren was normally present.

11. Titrations against rabbit and human thromboplastin showed a deficiency of thromboplastin in the patient's plasma.

12. The anticoagulant was directly antagonistic to anti-hemophilic globulin, completely neutralizing the effect of the latter upon known hemophilic blood.

13. Additional studies indicated that the

anticoagulant might be an antibody to some factor (such as anti-hemophilic globulin) in normal plasma, but this could not be confirmed by precipitin and complement-fixation tests.

After discharge from the hospital, the patient improved gradually and felt better. She was last seen on February 11, 1949, thirteen months after the onset of her illness. The hematuria had subsided, but there were still occasional slight ecchymoses. Her coagulation time was still prolonged (76 minutes) and the anticoagulant was still present.

Aureomycin and Chloromycetin in Brucellosis

With special reference to chronic brucellosis

HAROLD J. HARRIS

The diagnosis of low-grade chronic *Brucella* infection often lacks cultural proof. Evaluation of treatment methods is difficult. Any effective therapy which is free of deleterious effects and which obviates the need for hospital care is worthy of investigation.

AUREOMYCIN

Aureomycin hydrochloride was given orally to 110 patients, all but one with culturally-negative chronic brucellosis.

Dosage was 3.0 to 4.0 grams daily in the earlier cases and 2.0 grams daily in later cases, in 4 equally spaced amounts. Total dosage was from 18 to 25 grams in 7 to 14 days, if tolerated. Dosage in children was proportionately lower.

Side effects of a frequency, kind and severity not previously reported occurred in 48 of the 79 females (60.7 per cent) and in 6 of the 31 males (19.3 per cent), a notable difference between the sexes.

Headache, nausea, vomiting, epigastric pain, persistent diarrhea and anal irritation (with fissuring in 2) occurred in either sex. Mucous membrane manifestations of the mouth, throat and pharynx with perleche-

like lesions, occurred in 12 females and in 1 male, within 3 days in some. Vaginitis occurred in all of the 12 females, with slight bleeding in 3. Bladder irritation occurred in 8, fleeting urticaria in 3, dermatitis of the hands in 2 and slight generalized desquamation of the epidermis in 2. Peculiarly voracious and capricious appetites, especially for protein foods, were noted in many.

Thirty-four patients were unable to tolerate aureomycin for more than a few days but six were able to take smaller dosage of a more highly refined product.

The high acidity was presumed to account for some of the gastrointestinal and bladder manifestations, and destruction of the normal intestinal flora and/or allergy for the mucosal and dermal reactions.

Previously existing symptoms were temporarily aggravated in many patients.

Deleterious effects definitely ascribable to aureomycin were not noted. Agranulocytosis developed on the sixth day in a child who had been moribund at initiation of treatment; however, there had been a steadily developing leucopenia and neutropenia prior to treatment; recovery followed. Perforation of an unsuspected pre-pyloric ulcer, pos-

sibly due to direct irritation, occurred in one patient, with spontaneous healing.

Results of treatment cannot be fully evaluated until after prolonged observation. Of 55 patients who had adequate dosage and were observed for from 1 to 6 months following treatment 49 (89 per cent) made from partial to complete recovery; 23 required two or more courses. Six patients (11 per cent) showed no improvement.

In the one culturally proved case, there was rapid recovery but cultures were positive after each of two courses, with minimal evidence of relapse; following a third course cultures have remained negative for 3 months but minimal symptoms probably referable to *Brucella* infection continue to recur.

CHLOROMYCETIN

Chloromycetin was given to 25 patients (20 females and 5 males), all culturally-negative, in dosage of 2 to 4 grams daily with total dosage of 25 grams.

Side effects of appreciable degree occurred only in female patients previously intolerant of aureomycin; 5 of these had

recurrence of mucous membrane involvement and 2 had to discontinue it because of gastroenteritis. Relative freedom from side effects allowed use of chloromycetin in 13 patients who could not take adequate amounts of aureomycin. Fleeting sunburn-like erythema occurred in 3 patients, urinary frequency in 3.

Results of treatment were apparently comparable to those from aureomycin. Of the 14 patients adequately treated and observed, 11 (78.5 per cent) made from partial to complete recovery during observation periods of from 1 to 4 months; 3 (21.5 per cent) showed no improvement. Repeated courses were needed in 3 patients.

CONCLUSIONS

Aureomycin and chloromycetin favorably influence the course of brucellosis. It is premature to discuss curative effect. Chloromycetin is attended by fewer and less severe side effects. Male patients show greater tolerance. Effect on the intestinal flora is profound. Optimum dosage remains to be determined.

Response of Gastric-Dissolved Mucoprotein to Insulin: A New Test for Evaluation of Secretory Status of Fundal Glands and Integrity of Nervous Pathways to the Stomach

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In previous studies the authors showed that the dissolved mucin of the gastric juice was a mixture of at least two chemically different compounds, which they separated and called "dissolved gastric mucoproteose" and "dissolved gastric mucoprotein."¹ A chemical colorimetric method for quantitative determination of both fractions was developed,² and evidence was obtained to show that the mucoproteose was mainly a soluble split product of the enzymatic digestion of the visible surface epithelium mucus, while the mucoprotein fraction was the sec-

retory product of mucous cells of glands of the fundus and corpus of the stomach.¹

The authors showed also that the secretion of mucoprotein fraction was strongly influenced by vagal impulses and that humoral stimuli effective for acid secretion were almost devoid of any effect on secretion of gastric mucoprotein.² Insulin, injected intravenously in the dose of 16-20 units is a powerful stimulus for secretion of mucoprotein and after 40-60 minutes causes a sharp rise in mucoprotein concentration, the output exceeding the fasting

level 3 and more times. This rise coincides with the peak of hypoglycemic symptoms (drowsiness, dizziness, perspiration, fall in blood sugar) and is abolished if the nervous pathways to the stomach are divided or by atrophy or destruction of the mucous cells of gastric glands of the fundus and corpus area.

Three main patterns were observed in regard to mucoprotein and acidity response to insulin in over 50 tests performed on 40 individuals: 1) Positive pattern, characterized by a definite rise in mucoprotein (more than 60 per cent) and acidity; this is typical for normal stomach, nervous indigestion and gastro-duodenal ulcer. 2) Dissociated pattern, characterized by positive mucoprotein but negative or low acid response; this is found in subtotally resected stomach and in localized antral lesions, which impair the secretion of acid but leave intact the site of mucoprotein secretion, i.e. fundal area. 3) Negative pattern, characterized by a low or abolished response of mucoprotein and acidity to insulin; this is found in diffuse atrophic lesions of the gastric mucosa, in diffuse destruction of gastric glands by invading carcinoma, and as a rule after complete vagotomy.

Since the response of mucoprotein to insulin is abolished by vagotomy but not by subtotal gastrectomy, the mucoprotein test is also suggested for evaluating the completeness of vagotomy, especially in cases in which vagotomy is combined with subtotal gastric resection, and when it is impossible to decide whether a negative Hollander test depends upon vagotomy or resection itself.

Insulin test: The stomach under fasting conditions is emptied with Levine tube as completely as possible and 20 minutes later the second fasting specimen is again aspirated completely. Insulin is injected intravenously in a dose of 16 units (in thin and young patients—12 units only) and the stomach is emptied as completely as possible 20, 40 and 60 minutes after injection. Each of 5 specimens is tested for acidity and mucoprotein concentration. The mucoprotein and acidity curves are drawn on the basis of these determinations.

Volumetric office procedure for quantita-

tion of gastric mucoprotein. To 4 cc. of centrifuged gastric juice 2 cc. of 10 per cent trichloroacetic acid is added; after standing for a short time the mixture is centrifuged and the supernatant fluid is separated. Into a 15 cc. centrifuge tube graduated in 0.05 cc. or 0.1 cc. markings, 5 cc. of supernatant fluid and $7\frac{1}{2}$ cc. of acetone are placed. The content of the tube is mixed and the tube is set in the water bath or incubator at 56° C. for $\frac{1}{2}$ hour or at 40° C. for 1 hour. Then the tube is centrifuged for about 10 minutes, the supernatant fluid is briskly decanted and the remaining mucin precipitate is dissolved in 2 cc. of 1/10 N sodium hydroxide, using the wooden applicator for stirring. To this 3 cc. 1/10 N hydrochloric acid and 5 cc. distilled water are added, the content is mixed, left for 20 minutes at room temperature, and centrifuged exactly at 3000 RPM for 5 minutes (stopwatch). The volume of the precipitate is read on the graduations using magnifying glass, and the mucoprotein concentration is read from the table (interpolating intermediate values if necessary), as follows:

CALCULATION TABLE

<i>Volume of precipitate in cc. after 5 min. of centrifugation at 3000 RPM.</i>	<i>Concentration of gastric mucoprotein in mgm. per 100 cc. fluid gastric juice</i>
0.05	23
0.10	50
0.15	85
0.20	115
0.25	150
0.30	185
0.35	220
0.40	260
0.45	300
0.50	350
0.55	400
0.60	450

This simplified volumetric quantitation of mucoprotein was standardized on the basis of the original colorimetric tyrosine method published for quantitation of mucoprotein and mucoproteose fractions.²

CONCLUSIONS

Because the secretion of gastric mucoprotein is mainly dependent upon vagal influences and is almost independent of humoral stimuli, and because it depends on the status of effector organ, in this case the gastric glands of the fundus and upper corpus of the stomach, the testing of the mucoprotein response to insulin supplies the information

which cannot be obtained by means of other available tests, and is suggested as a new functional test of the stomach.

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*Electrolyte Abnormalities in Chronic Congestive Heart Failure;
Effects of Administration of Potassium and Sodium Salts*

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Plasma, edema fluid and urine electrolytes were studied during congestive failure. Plasma sodium was significantly below normal in twenty-seven of thirty patients. Plasma chlorides and potassiums ranged from below to above normal; chlorides, however, were relatively increased. Urinary sodium was low whereas potassium was high. Repeat measurements after recovery in five patients showed that the low sodiums had increased whereas chloride and potassium shifted toward normal.

During mercurial diuresis sodium chloride excretion increased but sodium in urine was usually hypotonic; chlorides, however, equalled or exceeded sodium. Potassium excretion increased fivefold.

The data indicated that failure is frequently associated with hypotonic extracellular fluid excessive in chloride and that during recovery, relatively more water, chloride and potassium are excreted than sodium. The possibility that some of the water excreted was of intracellular origin is also supported by the rise in the non-colloidal extracellular osmotic pressure which might draw water from cells.

Accordingly, sodium lactate was given to raise extracellular sodium and bicarbonate

concentrations, and potassium acetate to raise intracellular potassium and bicarbonate. Up to 100 mEq of each were administered orally for periods up to thirty days to six patients in failure. Mercurial diuretics previously required were omitted. Loss or no gain in weight occurred despite positive balances of sodium and potassium. Sodium excretion increased markedly although subnormal plasma sodium initially decreased further. Shift of water from intra- to extracellular compartments is thereby suggested.

Individual administration of the chloride and acetate of Na or K increased weight two to six kilograms; therefore mercurials were required after each single salt period. Simultaneous administration of sodium chloride and potassium acetate caused minimal weight gain despite positive Na, Cl, and K balances.

Extracellular hypotonicity may be associated with intracellular hypotonicity and depletion, hence separate readjustment of either compartment augments edema. Intracellular abnormalities may also be important in failure. Appropriate electrolyte administration may be of value in controlling edema in congestive heart disease.

*The Role of Proteins in the Pathogenesis of Renal Insufficiency**

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Reports from several sources have indicated that high molecular weight proteins (hemoglobin) and low molecular weight proteins (myoglobin, Bence-Jones protein) are capable of producing fatal renal insufficiency. Studies with hemoglobin and myoglobin have already established these substances as potent agents in the production of acute renal necrosis. A recent report incriminates the former substance as the cause of chronic renal insufficiency resulting from repeated renal insults, suggesting similar mechanisms in myoglobinuria. Intermittent injections with Bence-Jones protein in relatively small amounts has not resulted in renal impairment. No studies with large amounts of globulin have been carried out in either humans or animals. Accordingly, rabbits were injected with homologous (rabbit) gamma globulin procured through the courtesy of the Lederle Laboratories as Rabbit Anti-Pneumococcus Serum (Refined) which proved to be a 10 per cent solution

of almost pure gamma globulin.

The experiences with rabbits injected intravenously and intraperitoneally is presented. The quantity of urine voided in 24 hours was measured for globulin content. Concomitant blood counts and hematocrit readings were recorded in several instances. Histologic studies of the kidneys performed post-mortem revealed evidence of intrarenal hemorrhage due to the Silverman needle biopsy technique.

Following either intravenous or intraperitoneal injections of gamma globulin significant changes in the serum protein levels were observed. The details of individual experiments indicate a pronounced fall in the serum albumin as the globulin level rose (usually after 4 or 5 daily intraperitoneal injections of 50 cc. each). In one animal which received prolonged and repeated intraperitoneal injections, glomerular changes were observed.

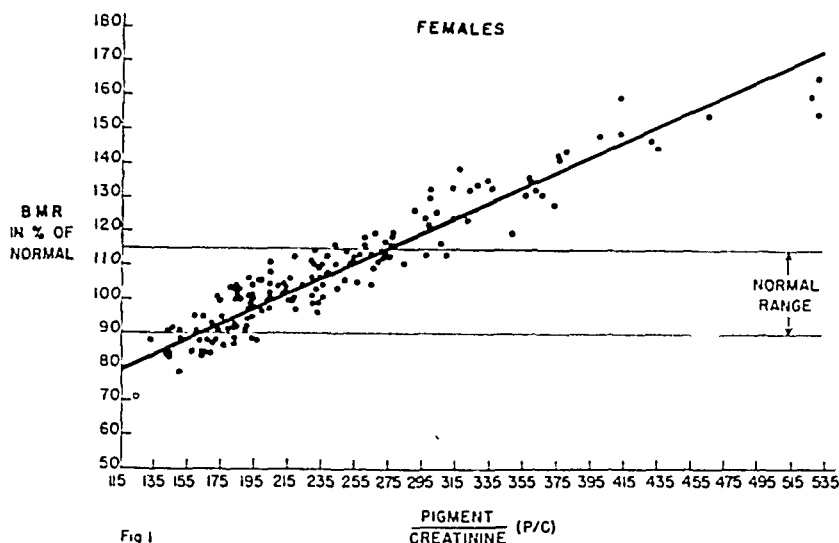
* Work done under a grant from the Joseph and Helen Yeamans Levy Foundation in memory of Miriam Levy Finn.

The Use of Urinary Pigment Excretion for the Measurement of Basal Metabolic Rate

JEFFERSON J. VORZIMER, IRA B. COHEN
and JULES JOSKOW, B.S., M.A.

The diagnosis and control of hyperthyroidism depends, to a large degree, upon an accurate determination of the basal metabolic rate. It is known that such conditions as neurocirculatory asthenia and apprehension may cause an increase in oxygen consumption which does not reflect the true basal metabolism. It is virtually impossible to obtain accurate BMR determinations in patients without teeth or with perforated ear drums. The existence of these conditions

which produce an increase in oxygen consumption rate, in the absence of an increased basal metabolism, frequently renders the accuracy of the BMR, as determined by the respiratory calorimeter, open to question. Since the determination of the true basal metabolism, and not a machine-measured increase in oxygen consumption, is of great importance in the diagnosis and control of thyrotoxicosis, the presence of any of the aforementioned conditions fre-

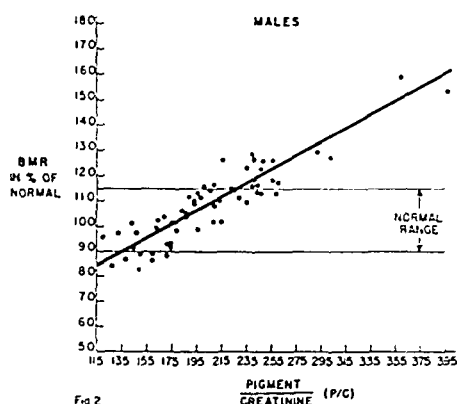


quently makes it impossible to determine true basal metabolism, with our present methods. The elaboration of a simple clinically-applicable procedure, which would serve as a measure of basal metabolism, independent of oxygen consumption at the time of the test, is, therefore, of great importance.

Drabkin¹ has shown that the output of the urinary pigment, urochrome, is remarkably constant from day to day, is independent of diet, but bears a relation to the level of basal oxygen consumption, and is therefore, a product of endogenous metabolism, being increased in hyperthyroidism and diminished after extirpation of the thyroid.

The daily creatinine excretion is extraordinarily constant for the individual, it is not influenced by ordinary exercise, and is practically independent of the protein level of the diet.

Ostow and Philo² reinvestigated the nature of the relationship between urinary pigment output and the basal metabolic rate. To correct for weight, height, and habitus of the subjects, the rate of pigment excretion was compared to the rate of creatinine excretion. This ratio (P/C) was found to parallel the basal metabolic rates



of patients to whom thyroid extract was administered.

The purpose of this investigation was to determine whether an accurate correlation existed between basal metabolic rates as determined by the respiratory calorimeter and the P/C ratio, and, if possible, to obtain a regression equation from this relationship. If a statistically valid equation could be derived, the P/C ratio could be applied wherever the accuracy of the BMR was in question.

The urinary pigment and creatinine concentrations are determined with a spectrophotometer.

Results obtained from 156 adult females and 57 adult males indicate that the P/C ratio can be used as a measure of metabolism in euthyroid and hyperthyroid states. Statistical analysis of the female series revealed a coefficient of correlation of 0.92. The regression line is: $BMR = 54.7 + 0.22 \text{ P/C}$. Analysis of the male cases revealed a coefficient of correlation of 0.88, the regres-

sion equation being: $BMR = 57.0 + 0.25 \text{ P/C}$.

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Treatment of Pernicious Anemia with Animal Protein Factor Concentrates of Bacterial Origin

LEO M. MEYER, NORTON D. RITZ, MANUEL ROWEN,
GEORGE BOCK and JULIUS RUTZKY

From the Department of Therapeutics, New York University Medical College

Animal protein factor concentrates were prepared from the aerobic fermentation of a non-motile gram-negative bacillus isolated from chicken feces. One cc. of one product (A.P.F. 60) had a biologic activity equal to "10 unit liver" when administered to chicks receiving a diet containing 70 per cent soy bean meal. In the *Lactobacillus leichmannii* assay the material had a somewhat lower potency (65% of "10 unit liver"). A second preparation (Normocytin) had a potency of 8 micrograms of B_{12} per cc. by *L. leichmannii* assay and equivalent to 10 micrograms of vitamin B_{12} per cc. by chick assay. Administration of A.P.F. 60 to 5 patients with pernicious anemia in relapse induced a satisfactory reticulocyte response in 4 instances, with an increase of Hb and

R.B.C. in all cases. Eight other persons with pernicious anemia in relapse treated with Normocytin showed a satisfactory reticulocytosis and an increase of Hb and R.B.C. Normal levels were observed in 6 cases. One patient from the original group treated with A.P.F. 60 was continued on Normocytin and also reached normal hematologic values. In all instances there was improvement and general well-being of the patients. Megaloblastic bone marrows were converted to normal states. Where neurological changes were present improvement was noted. There was no instance of progression or development of nervous system signs or symptoms. In two patients the Hb and R.B.C. remained below normal levels and are at present under treatment with vitamin B_{12} .

The Significance of RS-T Elevation in Acute Coronary Insufficiency

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and ARTHUR M. MASTER

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The concept of acute coronary insufficiency, as distinct from acute coronary occlusion, has been well established electrocardiographically and pathologically. It represents a disproportion between the demands of the myocardium for oxygen and nutritional elements, and the available supply in the coronary circulation. The mechanism may be inadequate blood flow, increased work of the heart, or impaired oxygenation of the blood. Coronary artery disease is usually present, but the heart may be normal.

There are various degrees of acute coronary insufficiency. Usually the inadequacy of blood or oxygen is transitory and easily reversible, as in simple anginal pain. Anatomical changes in the myocardium are absent or minimal and the process is a functional one. If the coronary insufficiency is severe or persistent, necrosis of the subendocardial layer of the myocardium occurs which may go on to extensive infarction.

In coronary insufficiency the electrocardiogram usually discloses RS-T depression and T-wave inversion, associated with the subendocardial ischemia or necrosis. Accordingly, the electrocardiographic changes may be transitory, or may persist for several weeks.

Coronary artery occlusion usually produces a massive infarct extending to the pericardium. As a result the electrocardiogram presents RS-T elevations and Q waves. The occurrence of such a pattern in coronary insufficiency, while noted occasionally in the literature, has been considered rare. However, in our experience the frequency of RS-T elevation in coronary insufficiency has been great enough to make its differential diagnosis from acute coronary occlusion clinically important.

Our material includes twenty-five cases of acute coronary insufficiency with RS-T elevation instead of RS-T depression. Serial electrocardiographic tracings were obtained, usually including unipolar precordial and extremity leads.

Five of these cases were examined post-mortem and no recent coronary occlusion was found. Clinically, all the cases lacked the corroborative evidence of infarction, i.e., elevated white blood count, abnormal sedimentation rate, and fever. Most of the patients had suffered previous coronary occlusion with infarction, usually of the posterior wall. Some, however, had no history or electrocardiographic evidence of previous occlusion with infarction.

In most of our cases the coronary insufficiency with RS-T elevation occurred spontaneously during ordinary activity, or under emotional stress. Other precipitating factors were paroxysmal tachycardia, hemorrhage and shock, and operative procedures including sympathectomy. The RS-T elevation was transitory, disappearing when the precipitating influence was removed. We were able to induce RS-T elevations by exercise and the injection of atropine and adrenalin.

Our data indicate that not infrequently an erroneous electrocardiographic diagnosis of coronary occlusion with infarction may be made in cases of transitory coronary insufficiency if the significance of the RS-T elevation in these cases is not appreciated.

The functional and reversible nature of the RS-T elevations is clearly demonstrated.

Our findings in humans confirm the experimental observations on epicardial and endocardial injury in animals, and contribute further to the understanding of the nature of myocardial injury.

* Dazian Foundation Fellow in Medicine. Sara Welt Fellow in Medicine.

stressed the great importance of a knowledge of pathology in surgery. He refined the abdominal suction tip which bears his name (1909) and was a pioneer in early postoperative exercises which he developed and wrote about while convalescing from an operation upon himself (1913). In 1927, recognizing the entity of psychosomatic syndromes, he arranged for regular ward rounds on his service by a leading psychiatrist from the Westchester Division of the New York Hospital. These are but a few of his extraordinarily important and trail-blazing contributions to surgery.

Dr. Pool's service in World War I was a distinguished one. Going to France with Base Hospital No. 9 (New York Hospital Unit) he became in turn, Chief Surgeon of Evacuation Hospital No. 1, Consulting Surgeon to the 5th Army Corps and finally, Consulting Surgeon to the 1st Army. He was discharged January 30, 1919 with the rank of Lieutenant Colonel and was awarded the Legion d'Honneur, the Distinguished Service Medal and a citation for "meritorious services" from the C.I.C., John J. Pershing.

This distinguished service in World War I was strikingly recalled in World War II when many of his observations, published after World War I—

"The Early Treatment of Gunshot Wounds"—Oxford Surgery, 1921 P745-775.

"Military Surgery of Joints"—Keen's Surgery, 1921 VII, 557.

"Surgery of the Soft Parts and Joints"—S.G.O., 1918 XXVII, 289.

"War Wounds, Primary and Secondary Suture"—J.A.M.A., 1919 LXXIII, 383.

"Treatment of Recent Wounds of the Knee Joint"—Annals of Surgery, 1919 LXX, 266

were of timely interest and of invaluable assistance to the recent World War II surgeon.

Dr. Pool was associated with many hospitals in a consultant capacity, among these being—

Home for Incurables

Central Islip State Asylum

New York Orthopedic Hospital

United Hospital at Portchester

French Hospital

Hospital for Special Surgery (R & C)
—where he was Surgeon in Chief, 1931-1936; Surgeon in Chief Emeritus, 1936-1949

New York Infirmary for Women and Children

Monmouth Memorial Hospital

Elizabeth A. Horton Memorial Hospital

North County Community Hospital

Presbyterian Hospital

New York Eye and Ear Infirmary

Harlem Hospital

St. Vincent's Hospital (N. Y. C.)

Despite the press of his exacting hospital duties and an increasing consulting practice, Dr. Pool was active in many professional societies and was accorded their highest honors:

New York Academy of Medicine:—
Fellow, 1904; Trustee, 1925-1934 and 1937-1941; President, 1935-1936.

New York Surgical Society—President, 1923-1925.

American Surgical Association—President, 1936.

International Surgical Society.

Southern Surgical Association.

American College of Surgeons—President, 1936.

Society of Clinical Surgery—President 1927-1929.

Detroit Academy of Medicine, Honorary Member.

In 1935 Governor Lehman appointed Dr. Pool Chairman of the Committee to rewrite the medical provisions of the Workmen's Compensation Act. This Act was in answer to the widespread medical abuses revealed by a former committee appointed by Governor Roosevelt. This Committee was an extremely important one and completely rewrote all the provisions of the Workmen's Compensation Act. The governor made the Committee's report his bill and it was passed without any amendments by the State Legislature. Since the passage of the bill, as drawn by Dr. Pool's Committee, it has been changed in only minor particulars and has served as a model for other states which have found it necessary to improve the medical provisions of their workmen's compensation laws.

Dr. S. S. Goldwater, New York City Commissioner of Hospitals, appointed Dr. Pool Administrative Consultant in Surgery for the City hospitals in 1934.

Dr. Pool was a life trustee of Columbia University, an Honorary Governor of the New York Hospital, a life Trustee of the Children's Aid Society and a former Trustee of St. Paul's School, Concord, New Hampshire. In 1944 he was awarded Columbia University Alumni Federation's Gold Medal for distinguished contributions to the University.

Dr. Pool loved sports and was an accomplished skater, above average golfer and played excellent tennis. For many years he looked forward to annual fishing and shooting trips. When he had the opportunity in his busy life he played as he had worked, with great skill, enthusiasm and with his characteristic will to win.

Dr. Pool's clubs were the Links (N. Y.), Piping Rock (L. I.), and the Harvard Club of which he was a former President. His life was crowded with activity and accomplishments.

Outside of his profession Dr. Pool's outstanding interest was that of a collector. Being a great, great grandnephew of Captain James Lawrence of "don't give up the ship" fame, he brought together over a period of years a remarkable collection of memorabilia and other objects concerning Captain Lawrence. Today this collection may be seen in one of the galleries of the New York Historical Society.

It is rare for a doctor to receive and deserve an editorial in a leading New York paper. The Evening Sun, on April 13, 1949, paid Dr. Pool this superb tribute:

"It would be impossible to estimate the number of persons who owe their lives to Dr. Eugene Hillhouse Pool. Even a complete roster of all who came under his hands as patients would only begin to tell the story. To those would have to be

added the patients of thousands of men, surgeons today in all parts of the world, who gained their skill from watching the amazing hands of this master surgeon and from listening to his sound advice on how best to repair broken bodies. Among a whole generation of surgeons there is no prouder boast than that of having been a pupil of Eugene Pool, that extremely strict taskmaster who demanded rigid perfection in his students but who spared nothing in seeking to attain it himself. If his capabilities in the operating room alone were taken into account, the world would be heavily in his debt. Coupled with them, however, were an unswerving integrity, a tremendous interest in all matters pertaining to the medical profession and the fine instincts that mark the true gentleman whatever his field of endeavor. As President of the Academy of Medicine in a period when it was seeking to shape its future course, he did much to set it on the road to its present high estate. A man who habitually shunned the spotlight, Dr. Pool on his death left little material for biographers. More important, he left a shining example for doctors, present and future."

Dr. Pool was divorced from his first wife, Mrs. Esther Hoppin Pool, in 1930 and his second wife, Mrs. Kitty Lanier Hariman Pool, died in 1936. Surviving are his third wife, Mrs. Frances Saltonstall Pool, two sons by his first marriage, Dr. J. Lawrence Pool and Beekman H. Pool, a brother, Harry Henry Pool and a sister, Mrs. Sophie Duer.

In his death on April 9, 1949 the profession lost a great leader, the community a great force, his associates a great friend.

"The soil out of which such men as he are made is good to be born on, good to live on, good to die for and good to be buried in."

FRANK J. MCGOWAN

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE



AUGUST 1949

ALLERGY AND ANTIHISTAMINE THERAPY*

A Review

MARY HEWITT LOVELESS

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and

MILTON DWORIN

Research Fellow in Medicine (Allergy), Cornell University Medical College

FOR the allergist, the advent of the histamine antagonist has two appeals; viz., it offers a very satisfactory means of alleviating certain allergic symptoms, and it may throw light on the fundamental mechanism of allergy. Ever since Dale and Laidlaw¹ drew attention to the similarity between the experimental shocks of histamine and of anaphylaxis, efforts have been made to synthesize substances antagonistic to histamine. In the meantime Code,² Rocha é Silva,^{3,4} Dragstedt,⁵ and others have presented additional evidence for the role of histamine in allergy as well as in anaphylaxis. The earliest reports of success in the search for antihistamines came from Bover's laboratory when the so-called Fournieu series of synthesized phenolic ethers were described

* Read at the 21st Graduate Fortnight of The New York Academy of Medicine, October 11, 1948.
From The New York Hospital and the Department of Medicine, Cornell University Medical College.

in 1933⁶ and in 1939.⁷ Although these products exhibited definite powers to antagonize histamine *in vitro* and *in vivo*, they proved too toxic for human use. The difficulty was first surmounted in Antergan which Halpern⁸ tested in man during 1942. This success of the French school motivated a further search for superior agents by American workers, and resulted in the introduction of Benadryl⁹ and of Pyribenzamine¹⁰ in 1945. At the time of the present writing, over a dozen such agents are available to the medical profession.

The aim of this presentation is to summarize the pertinent observations concerning these drugs and to present our own experience with a number of them in the control of hay fever.

PHARMACOLOGY

In reviewing the chemical and pharmacological properties of anti-histaminic substances, certain rules laid down by Staub⁷ have been found to govern the relationship between chemical structure and physiological activity. In general, the agents can be placed in one of two categories; (1) amines represented by the formula



R_1

and exemplified by Antergan, PBZ, Neoantergan, Hetramine, Antistine and Thephorin; and (2) ether types represented by the formula



exemplified by Benadryl and Linadryl. In these formulae,

R represents phenyl or substituted phenyl

R_1 represents alkyl or aralkyl

R_2 represents phenyl or substituted phenyl

The amine or first group is said to be more "specific" against histamine shock, whereas the ether type is more effective against histamine-induced asthma.

The pharmacologic effects of the typical histamine antagonist have been summarized by Loew.¹¹ It blocks the bronchio-constriction caused by histamine, negating as many as 1500 lethal doses of histamine for the guinea-pig; it prevents the histamine contraction of both intestinal and uterine muscles; and it antagonizes the drop in blood pressure which follows histamine administration in the experimental animal. Not only does the antagonist exert these influences on the histamine reactions of animals but, in several species at least, has a parallel effect on anaphylaxis.

The use of the antihistamine as a pharmacological tool has, therefore, provided evidence which establishes even more firmly the concept that histamine plays a role in anaphylaxis in some animals.

In the case of man, the value of antihistamines has been amply established for certain allergic states (including the skin-test response). It is pertinent, Loew comments, that favorable reports have thus far been restricted to allergic diseases and a few other conditions where histamine is a suspected etiological agent. The implication is thereby given that histamine is involved in several types of human hypersensitivity. The low order of efficiency found for asthma, on the other hand, suggests that its mechanism differs from that of hay fever.

The antihistamines do not achieve their effect, it appears, by eliciting pharmacologic effects which oppose those of histamine. They differ basically, therefore, from epinephrin. In these agents, as Gilman¹² states, "we do not have compounds that cause, by themselves, any prominent degree of muscular relaxation [in the bronchi and gastrointestinal tract] or have any effect on the peripheral vasculature in their own right. We are dealing here not with physiologic antagonists, but rather with a type of blocking agent. The mechanism of action is similar to that by which atropine can block the effects of acetylcholine or of cholinergic nerve impulses. It does not prevent the release of histamine, but rather it prevents the histamine from gaining access to the receptor mechanism in the cell and there exerting its characteristic effects. I think if one keeps that mechanism in mind, many of the rather paradoxical failures of antihistaminic therapy will explain themselves." Gilman's remarks are in keeping with the observation that the gastric secretagogue effect of histamine is not antagonized by the new drugs—a situation which suggests that it is the receptor cell rather than histamine itself which is blocked when the drug exerts its typical influence.

TOXICITY

In animals, toxic doses of all the antihistamine drugs lead to central stimulation as evidenced by hyperexcitability, tremor and convulsions. The commonest side effect in man, on the other hand, is sedation. It is pertinent that the acute toxic effects of the antihistamines appear unrelated to any physiological mechanism involving histamine.⁹ No signs of chronic toxicity have been observed in the blood, urine, parenchymatous organs, nervous system or bone marrow of man or animal.

THERAPEUTIC AND UNTOWARD EFFECTS OF ORAL
ADMINISTRATION IN MAN

Dosage: Pyribenzamine, Neohetramine, Linadryl and Neo-antergan are usually dispensed in doses of 50 milligrams, whereas 100 milligrams are prescribed for Antistine, and 25 milligrams serve for Trimeton, Thephorin and Decapryn. Hydryllin is the proprietary name of a tablet containing 100 milligrams of Aminophyllin and 25 milligrams of Benadryl. Antergan has been used by a single investigator in doses of 40 to 80 milligrams daily. Although no reference will be made in the present writing to routes other than oral, certain of the antihistamines have been successfully given intramuscularly,¹³ intravenously¹⁴ and by local inunction (PBZ¹⁵ and Thephorin¹⁶). The interval advocated between doses is ordinarily not less than four to six hours, depending upon the recurrence of symptoms. At times, double or half the conventional dosage is suitable.

THE THERAPEUTIC AND SIDE EFFECTS OF 11 HISTAMINE
ANTAGONISTS: A SURVEY OF THE LITERATURE

Therapeutic Efficiency in Man: Table I is a composite of published results from the use of 11 histamine antagonists in eight common disorders of presumed allergic origin.¹⁷⁻¹⁸ The investigators are indicated by the reference numbers listed above each drug. As indicated by the averages given at the bottom of the table, the drugs in general show their greatest effectiveness in cases of urticaria and angioneurotic edema, 82 per cent of some 1500 trials bringing relief. The next most responsive condition was extrinsic allergic rhinitis (or hay fever) with a therapeutic index of nearly 75 per cent among 7000 cases. Contact dermatitis, atopic dermatitis and vasomotor rhinitis responded somewhat less spectacularly, between 60 and 65 per cent of tests proving successful. Since the number of observations on contact dermatitis is small, it is possible that its future position in the list of susceptible conditions may shift. This remark applies also to pruritus associated with disorders other than urticaria, for only 85 such cases have been observed under antihistaminic therapy. On the other hand, bronchial asthma of either extrinsic or intrinsic origin has been widely treated with the new drugs and takes its position low in the list, with a therapeutic index of less than 50 per cent. (Our failure to distinguish between the extrinsic

TABLE II—SIDE REACTIONS FROM 8 HISTAMINE ANTAGONISTS

INCIDENCE OF COMMONEST TYPES OF SIDE REACTION																			
General Incidence of Side Reactions			Sedation		Gastro-intestinal		Central Stimulation		Dizziness		Headache		Vascular		"Allergy"		Miscellaneous		
ANTAGONIST	Total No. Patients Observed	Per Cent with Side Reactions	Cases	%	Cases	%	Cases	%	Cases	%	Cases	%	Cases	%	Cases	%	Cases	%	
Neohetramine	21,47	509	58	11	29	6	21	4	2	1½	4	1	0	0	13	3	2	0.4	
Antistine	10,21,44	221	20	9	19	9	3	1	3	1	1	½	1	½	1	½	5	2	
Thephorin	10,30-32,34-38	1,589	54	3	82	5	196	12	22	1	25	1	17	1	9	0.6	36	2	
Pyribenzamine	10,28,29	2,058	242	10	181	9	63	3	67	3	55	3	19	1	19	½	38	2	
Trimeton	10,21	171	49	29	3	1	6	4	0	0	6	2	0	0	0	0	2	1	
Decapryn	10,24	157	56	36	3	2	4	3	5	3	3	2	0	0	1	½	6	4	
Nco-antergan	10,21,42	255	100	39	15	6	0	0	4	2	4	2	0	0	0	0	5	2	
Benadryl	20	655	315	48	52	8	65	10	46	7	0	0	19	3	6	1	47	7	
Total	5,615	894		384		358		149		98		56		49		141		
Average Per Cent		16		7		6		3		2		1		1		3		

and intrinsic forms is referable to this common practice among the authors reviewed. It is our impression,²⁹ however, that this is irrelevant in the case of the antihistamines, since seasonal forms have proved to be almost as unyielding as the idiopathic, or infectious, types.) Although very few observations were to be found for migraine, this disorder appears to be another which responds poorly to the antagonists.

The overall efficiency of each of the 11 drugs was crudely judged by calculating the general incidence of relief for all eight of the allergic disorders. The results are indicated in the right hand column of Table I, the drugs being listed in order of their average efficiency. Several of these figures should be accepted provisionally since the observations behind them are too limited for final judgment. Antergan and Linadryl fall in this category, fewer than 200 trials being involved. Among the other agents Trimeton, Decapryn, PBZ, Thephorin and Benadryl appear to be more effective than the average of 66 per cent, shown at the foot of the last column. Neo-antergan, Hydryllin, Antistine and Neohetramine, on the other hand, fall below this crude standard.

In view of the fact that over half the published observations have dealt with hay fever, it is not surprising that the sequence in column 3 resembles that of the column for overall efficiency, Antergan ranking first, Trimeton second, and so on. There are some shifts in this order for the columns headed "Urticaria" and "Atopic Dermatitis," reflecting either unreliable data or selectivity in drug effect. Since the results for Antergan and Linadryl are based on one publication only, no evaluation can be made until other investigators report on these drugs. Neither bronchial asthma nor intrinsic rhinitis appeared to show any discrimination among the different drugs. The number of data on contact dermatitis, pruritus and migraine are insufficient for final conclusions. This difficulty and others encountered in the appraisal of the antihistamines will be touched upon later in the article.

Side Effects: A search was made for reports of side reactions among the publications reviewed in Table I. Although information was not always available, adequate material was at hand to determine the incidence as well as the type of side reactions for 8 of the drugs. Table II refers only to those publications which stipulated the nature of the side effects.

Of the various untoward responses, sedation was the most prom-

inent. Whereas the average incidence for all 8 drugs was 16 per cent, as shown at the foot of the column, it will be noted that Benadryl acted as a soporific in 48 per cent of trials. At the other extreme was Thephorin, which sedated only 3 per cent of its consumers. Decapryn, Neoantergan and Trimeton also possessed this tendency in rather high degree whereas Antistine, PBZ and Neohetramine caused drowsiness in but one out of ten trials. It should be remarked that sedation is not always an undesirable side reaction, being of value in pruritus and in insomnia due to allergic states.

Gastro-intestinal disturbances were next in order of frequency, being noted in 7 per cent of all the trials. Patients with disorders of the digestive tract should probably avoid Antistine, PBZ and Benadryl and choose antihistamines of low gastric toxicity; viz., Trimeton and Decapryn.

Under "Central Nervous System," we have included such manifestations of central stimulation as: general irritability, nervous tension, insomnia, palpitation, agitation, paresthesias, genitourinary disturbances, chills, blurred vision and diplopia. One or more of these were encountered in a total of 6 per cent of cases. Several investigators noted that Thephorin was particularly prone to cause nervousness and insomnia, a situation which is consistent with its high incidence of central stimulation (12 per cent).

Dizziness was next in rank, being encountered after 3 per cent of trials with all drugs. Benadryl, with an incidence of 7 per cent, was the chief offender, Decapryn and PBZ rating second with 3 per cent.

It will be seen that Benadryl produced no headaches in 655 trials and that Antistine caused but few. The general incidence of cephalalgia was not high, however, PBZ topping the list with an incidence of 3 per cent.

Less frequently encountered were vascular disturbances (including tachycardia, tendency toward bleeding, edema of skin, pallor, tinnitus, syncope, sweating and flushing). The accumulated incidence of such complaints amounted to about 1 per cent.

So-called allergy to the drugs was reported for an equal proportion of the patients. The disturbances consisted of eruptions, cough and dyspnea. We have recently seen generalized eruptions in two subjects following the ingestion of PBZ.

Less frequently described in the literature were a host of miscella-

TABLE III—RELATIVE THERAPEUTIC AND TOXIC EFFECTS OF VARIOUS HISTAMINE ANTAGONISTS

<i>HISTAMINE ANTAGONISTS</i>	<i>Incidence of Relief</i>		<i>Incidence of Side Effects</i>		<i>Rank</i>
	<i>No. of Patients</i>	<i>No. Re- lieved (%)</i>	<i>No. of Patients</i>	<i>No. with Side Effects (%)</i>	
Antergan ¹⁷	126	86	140	25	(5)
Trimeton ^{18,20*,21,22*}	671	76	398	25	(5)
Decapryn ^{19,23*,24}	306	75	157	41	(8)
Pyribenzamine ^{19,20*,24*,25,26*,27-29}	4,942	70	2,276	25	(5)
Thephorin ^{19,30,31,32,33*,34-38,39*,40*}	1,877	69	1,559	24	(4)
Benadryl ^{20*,21*,26*,29}	2,058	67	655	61	(9)
Neo-Antergan ^{19,20*,21,25,26*,27,41*,42}	893	61	649	29	(6)
Hydriyllin ^{20*,25,27,43}	1,062	56	233	36	(7)
Antistine ^{19,21,25,27,44,45*,46*}	492	55	417	18	(3)
Neohetramine ^{21,25,47}	624	52	630	13	(1)
Linadryl ⁴⁸	139	52	250	17	(2)
<i>Total</i>	13,190		7,364		
<i>Average</i>		66		27	

* Used for "Therapeutic" data but, omitted from "Side Effects" on this table.

neous conditions, such as early or excessive menstruation, decreased libido, impotence, emotional depression, sore throat, fever, oral anesthesia, dry mouth, muscular twitchings and incoördination. The sum total of such reports amounted to 3 per cent for all drugs.

A larger set of figures was available for toxicity without reference to the type of side reaction. The data for an additional 1749 cases have been added to those of Table II and listed for all 11 drugs to make Table III. The purpose of this table was to afford a quick comparison among all drugs for toxic as well as therapeutic characteristics. Added to the side-effects data, therefore, are summaries of all therapeutic information found in the literature. The agents have been listed, in order of their therapeutic rank. The toxicity rating is indicated in the right-hand side of Table III.

It will be seen that those three agents which possessed the lowest therapeutic power (Antistine, Neohetramine and Linadryl) showed

also the lowest toxicity. In the middle bracket were Antergan, Trimeton, PBZ and Thephorin, which produced side reactions in every fourth patient. The average incidence of side reactions was 27 per cent for all 11 drugs, the figure for Neo-antergan approximating this incidence. More toxic than the preceding were Hydryllin, Decapryn and particularly Benadryl.

Attempts to Improve Methods of Appraisal of Drugs: Although the foregoing analyses of clinical data from the literature throw some light on the relative desirability of the various drugs, a more reliable evaluation could be made if some of the many variables could be removed from the test. One of these is represented by the multiplicity of observers, each of whose judgment probably colored the appraisals. Arbesman,²⁵ for example, recorded only 30 per cent of patients relieved by Antistine, whereas Kaplan and Erlich's⁴⁶ figure for the same test was 92 per cent. If a single observer could evaluate a number of different drugs, this particular variable could be largely eliminated.

An even greater extraneous factor is involved when one attempts, as we have done, to estimate the efficiency of an antagonist by lumping together the results of its use in sundry allergic disorders. When a new drug is examined for its influence on hay fever, for example, and only in a limited way is studied for its effect on asthma, a higher therapeutic index is to be expected than if most of the trials are made in asthmatic patients, since it is established that bronchial allergy responds poorly to the antihistamines.

In an attempt to circumvent such variables, we recently evaluated six antagonists by alternating their use in a group of 113 patients with a similar clinical disorder, ragweed hay fever. The data were segregated not only according to the intensity of their symptoms but also according to the degree of relief afforded, as well as to the type and severity of side reactions. It was hoped that these more rigid criteria might bring to light superiority of any one antihistamine.

The results of these trials can be visualized in Graph A, which indicates the desirable effects in its upper half and the untoward reactions in its lower section. It will be seen that PBZ and Trimeton possessed almost identical powers to control seasonal hay fever, whether judged by their capacity to afford complete or partial relief. This is perhaps more readily visualized in the white areas of the upper part of the graph, which show that failures occurred in only 18 per cent of the

group after either drug. Trimeton offered complete relief of severe hay fever in a somewhat greater percentage of trials than did PBZ.

The untoward responses, dealt with in the lower half of the graph, were of a severe order in an equal proportion of cases given either drug, whereas somewhat fewer mild reactions were noted after Trimeton than after PBZ. On the basis of these observations, one might conclude provisionally that Trimeton was the slightly superior agent for hay fever.

In making comparisons between Neo-antergan and Decapryn, the similar therapeutic potencies of these two drugs must be weighed against the definitely greater toxicity of Decapryn. The dosage of the latter should probably be modified because of this frequency of side reaction. In the case of the remaining two pharmaceuticals, Thephorin appeared to carry about the same ratio of undesired responses as Antistine but showed a greater therapeutic efficiency. Indeed, for mild attacks of hay fever, Thephorin approximated the control noted for Decapryn and Neo-antergan.

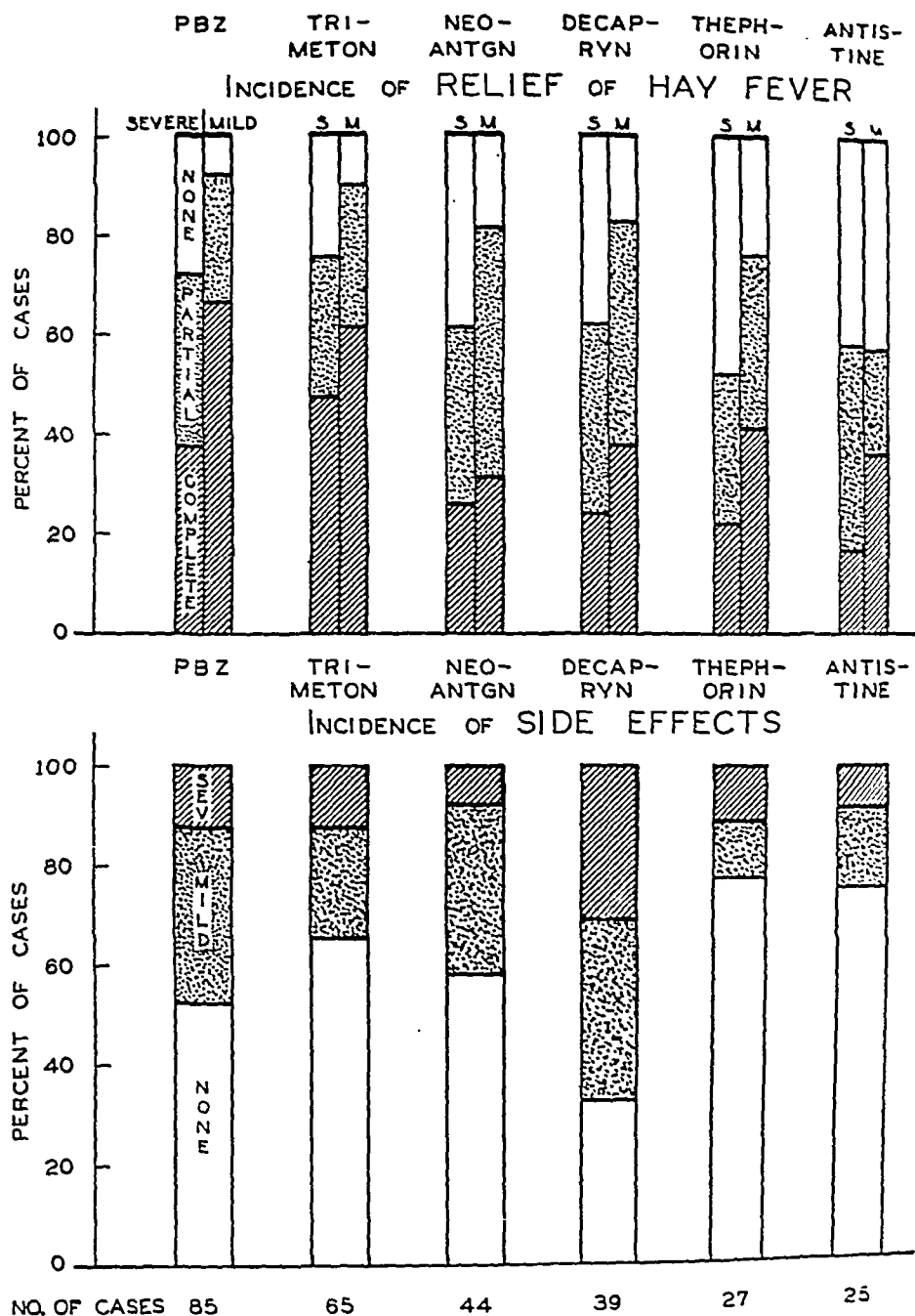
It is of interest in passing to observe that the side reactions of the antihistamines are in general of a mild order, as revealed by the dotted areas of the lower half of the graph.

When comparison was made between the order of therapeutic efficiency of the 6 drugs given our hay fever group and the order noted for the same agents in our review of the literature covering all forms of allergy, it was found that Trimeton ranked first in both series, whereas Antistine took last place. PBZ was listed second in the hay fever experiment, third in the overall trials. Decapryn and Thephorin ranked above Neo-antergan in the literature, below it in our series. Regarding the side effects, Antistine and Thephorin had the best records in both surveys, whereas Decapryn and Neo-antergan caused the most trouble. The relative positions of the other agents were at variance in the two tables.

Graph A is presented not only because it offers a quick means of judging the relative merits of different agents in hay fever, but also because it offers a simple form of presenting rather complex data. This handling might be adopted by future investigators to standardize their information and make possible the eventual selection of superior antihistamines. Placebos could of course also be used concurrently with the drugs to evaluate the psychic factor.

Since the appraisal of a dozen or more antihistamines is too large a

THERAPEUTIC AND SIDE EFFECTS OF 6 ANTIHISTAMINIC DRUGS USED BY PATIENTS WITH HAY FEVER



Graph A

task for any individual to carry out single-handed, it is in order for a group of large clinics to undertake a joint, integrated attack of the problem. It is hoped that some of our suggestions for classifying the allergic disorders and the drug effects will prove useful to those who may organize such a project. At the same time optimal dosage should also be determined for the various antihistamines, since the doses in present use are probably too large for the more toxic preparations and too small for those with a low therapeutic index.

SUMMARY AND CONCLUSIONS

1. The histamine antagonists effectively negate many of the effects of histamine, anaphylaxis and allergy. In man they are particularly helpful as symptomatic aids in urticaria and hay fever, are also of definite but less value in contact and atopic dermatitis as well as in vasomotor rhinitis. Their influence on non-urticarial pruritus, asthma and migraine is less impressive.

2. Analysis of the therapeutic effects of 11 antihistamines reported in the literature reveals that among some 13,000 trials, Trimeton, PBZ and Thephorin offered the most satisfactory control of sundry allergic symptoms without an undue number of side reactions.

3. Final choice of the ideal antagonists, however, will have to await evaluation of multiple agents in similar groups of allergic patients under standard conditions and criteria, preferably through the concerted efforts of several large clinics. A small group of our hay fever cases, evaluating 6 antihistamines by alternation, found Trimeton and PBZ the most satisfactory from the viewpoints of therapeutic control and toxicity.

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MEDICAL AND SURGICAL TREATMENT
OF PEPTIC ULCER*

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LITTLE that I can say on this time honored subject can be other than what I am sure could and would be said by any one of numerous outstanding physicians or surgeons in this city. The only novel aspect of such a talk lies in the suggestion that a physician, primarily interested in internal medicine, has been invited to present his views on both the medical and surgical aspects of this problem. It was for this reason alone that I was tempted by the flattering invitation from the Academy of Medicine, even at the risk of being thought impertinent and somewhat "out of bounds."

The orthodox story of peptic ulcer can be told quickly. By definition it is a chronic recurrent disease of unknown etiology. Characteristically peptic ulcer occurs in the proximal portion of the duodenum, but may be found in any portion of the stomach, the lower duodenum, the distal esophagus, in Meckel's diverticulum, rarely in the jejunum, and not infrequently in or near anastomoses between the stomach and the intestinal tract. Although the etiology is not known, certain facts have become clear in the course of many years of clinical experience with this malady. These facts have moulded the various therapeutic measures that are now currently employed in attempting to control the disease and to prevent recurrences. To date the word "cure" must be used with circumspection inasmuch as no method of treatment yet devised, however radical, can guarantee invariable, lasting success.

I should first like to discuss the medicinal treatment of uncomplicated duodenal ulcer. Because of the fact that so-called gastric hyperacidity is the general rule in duodenal ulcer and because of the added fact that experimental observations in man and in animals indicate the importance of this factor in conditioning ulcer activity

* Read October 13, 1948 before the 21st Graduate Fortnight of The New York Academy of Medicine.

and ulcer symptomatology, antacid therapy has long held a prominent place in the treatment of the disease. The declared purpose has been to neutralize gastric acidity and thereby reduce or abolish peptic activity. Complete neutralization is never obtained by any such means, except for limited periods of time. However, the pH of the gastric contents can be raised to a point at which peptic digestion is reduced to a minimum, and this state can be maintained for prolonged periods of time, provided the patient can and will tolerate the frequent and long continued administration of one or another of the various antacid preparations that are in favor at any given time. These range from simple bicarbonate of soda through the heavier free alkalis to such nonabsorbable preparations as magnesium trisilicate, the various colloidal preparations of aluminum, and the latest comers,—the resins. All are effective in reducing gastric acidity, and all are effective in controlling to a greater or lesser degree the pain or discomfort associated with most uncomplicated ulcers. The relief obtained by their use varies in duration and degree in individual cases, but there can be no doubt that they are useful aids as symptomatic measures, and their use may hasten the healing of active lesions. There can also be little doubt that they accomplish very little if anything in the prevention of ulcer recurrences. Certain disadvantages should be mentioned. Bicarbonate of soda, if taken in effective doses, can produce alkalosis, although this statement applies primarily to those individuals with ulcer who have an associated derangement of renal function. In those patients with prolonged massive hemorrhage or with real malnutrition secondary to partial pyloric obstruction, the use of sodium bicarbonate may provide the necessary factor to produce tissue edema in the presence of a lowered serum protein. The prolonged use of this antacid or of others which produce an alkaline urine may occasionally provide the basis for the formation of renal calculi. The continued use of many of these preparations may derange bowel activity to a point where diarrhea or severe constipation becomes a troublesome symptom. Thus magnesium, and less frequently soda bicarbonate, may increase bowel activity to a very undesirable extent. Calcium carbonate and some of the aluminum hydroxide preparations may cause constipation and even fecal impactions. Finally it may be stated that the administration of alkaline or antacid preparations at frequent intervals and over long periods not uncommonly becomes a monotonous and at times distressing

form of treatment to many patients. Under such circumstances they prejudice the success of otherwise effective treatment by constituting a source of increasing annoyance to an already disturbed individual. Their intensive use is not absolutely essential to the successful handling of the majority of ulcer patients.

Attempts to control gastric secretion by medical means have included many other measures such as the use of detergents, animal and vegetable mucins, x-radiation, hormonal therapy and the belladonna alkaloids. The detergents and mucins, although effective in adequate doses in diminishing peptic activity in the stomach, defeat their own purpose by the fact that they are extremely distasteful remedies from the patient's point of view. X-radiation, in order to be effective, involves certain risks, and at the best produces only temporary secretory changes. Hormonal preparations, such as pituitary snuff, antuitrin S, and the like, have failed to produce results that are of more than academic interest. Enterogastrone has not yet been purified. The available preparations have been used largely for investigative work, and sufficient time has not yet elapsed to permit a complete evaluation of this work. There seems to be little doubt that the prolonged parenteral use of this product has resulted in a reduction of gastric secretory and motor activity, with a beneficial effect on some ulcer patients. It is not yet known whether its use over many months will largely prevent ulcer recurrences, but recurrences have been noted during the course of continuous enterogastrone therapy by Sandweiss, ourselves and others. Alone of the therapeutic measures mentioned to date it offers the hope of usefulness in the prevention as well as the immediate healing of peptic ulcers.

Atropine and its derivatives affect secretory and motor processes in the stomach by reducing vagal stimulation of that organ. When *tolerance* doses are employed, either by mouth or by injection, ulcer activity can frequently be controlled by their use. Their action is temporary, but no more so than that obtained by the use of antacids. Actually the effects of proper single doses of atropine or belladonna can be noted over as long or longer periods of time than those due to single doses of many antacids. The use of atropine or its derivatives as effective agents in the treatment of patients with active duodenal ulcers is fully justified by clinical results and by careful pharmacological studies. Hypersecretion and hypermotility are both reduced, although

neutrality of gastric contents, of course, is not achieved. When combined with the usual dietary measures these anticholinergic drugs are frequently to be preferred to antacids because of the fact that their use by mouth involves fewer medications per 24 hours. Full tolerance doses, just short of dryness of the mouth or visual disturbances, are the only effective doses,—a point frequently overlooked. The disadvantages accruing to their use are well known. In addition to the two unpleasant symptoms already mentioned, headaches, disorientation, and difficulties in bladder control may occur,—objections that are particularly pertinent to the older age group. In the average case these unpleasant symptoms do not develop. It should be added that in active ulcers with a great deal of pain and moderate gastric stasis, subcutaneous atropine, given at regular intervals, may be of great help in tiding over a rather critical period. The synthetic preparations syntropan and trasentin are more expensive, much less reliable, and usually of little value as substitutes for atropine or belladonna. Incidentally, the frequent success attendant upon the proper use of atropine or belladonna preparations offers one solid reason for the use of vagotomy in carefully selected cases. In fact, the successful results obtained with atropine might be properly classed as medical vagotomies.

A third type of medication derives its therapeutic indications from the known relationship between states of emotional tension and gastric secretory and motor activity. Sedation, as provided by drugs such as phenobarbital, can at times be of profound help in controlling the symptoms of an active ulcer. It is a commonplace observation that ulcer patients can be symptomatically improved in short order if their emotional disturbances can be effectively controlled. I shall refer to the psychotherapeutic implications of this statement later. At least a partial block can be thrown across the abnormal stream of impulses going from higher centers through the hypothalamic area to those autonomic pathways supplying the stomach by the use of oral or subcutaneously administered barbiturates. In simple situations repeated, moderate doses of phenobarbital by mouth can be helpful to an important degree. In those patients whose ulcer pain and their own emotional unrest form a vicious cycle making symptomatic control very difficult, the regular, periodic subcutaneous use of sodium phenobarbital and atropine over a period of days may prove a therapeutic maneuver of major importance.

Other types of medication should be briefly mentioned, largely for dismissal. The use of histidine by parenteral injection has by now been thoroughly discredited. The fact that it is still used suggests either a rather blind hope on the part of a few physicians or a desire on the part of another few to indulge in wishful thinking at the expense of the patient whose weekly monetary contribution for treatments soothes the protests of critical professional judgments. In this regard it is wise to recall the excellent work of Sandweiss who obtained equally good or better results from the parenteral administration of sterile salt solution as from injections of histidine. The lessons to be derived from such careful observations are clear. Therapeutic methods which depend on gadgets, complicated maneuvers, injections, and expensive procedures may impress and temporarily help a patient afflicted by chronic disease. Their use is unjustified not only because of the fact that they are usually unnecessary, but also because they lead to ill considered thinking by the physician who uses them.

The second therapeutic approach to the problem of ulcer is that of diet. Numerous variations have been evolved which differ in detail but agree in one fundamental and common feature,—that of frequent, periodic small feedings. The Sippy diet, which frequently has been modified almost beyond recognition, depended on hourly feedings, day and night, of a milk and cream mixture. On the half hour heavy doses of alkalis were employed. Thus the patient theoretically had something by mouth 48 times in 24 hours. The milk and cream mixture, with its high fat content, resulted in an inhibition of gastric secretion; the milk proteins acted as a buffer substance as well as a supply of nitrogenous material. The addition of alkali tended to maintain a low level of secretory activity in the stomach. The regime, therefore, satisfied many of the requirements necessary for ulcer healing. It had certain real disadvantages. Many patients were unable to tolerate the cream feedings because of distaste or actual nausea. A further number found the interminable half-hourly feedings of milk and cream or alkali so distasteful after a few days that they refused to continue to follow the full schedule. As a result various changes have been made either in the type or variety of food, the frequency of feedings, or the constant alkali therapy. It is fair to say that practically all dietary measures have been successful in uncomplicated cases, provided that certain simple requirements are met. These requirements are common to all

ulcer regimens. They may be summed up briefly as follows. In uncomplicated duodenal ulcer any very simple nonbulky, nonirritating food that is fed frequently in small amounts, on time, is satisfactory. In an acute ulcer, hourly feeding intervals during the day, and two-hourly intervals at night, are usually effective in providing protein buffer, fat, and calories. Milk is still the best single food, but in most instances can be alternated with other simple foods to relieve monotony. As treatment progresses toward symptomatic improvement and healing, the intervals can be prolonged until the patient is on a simple six-meal bland diet. Frequently rest and dietary measures alone are entirely effective without the use of any medication.

Because a properly planned dietary regime can provide antacid, calories, and nitrogen, it has been inevitable that certain very special regimens have been devised for the treatment of ulcer embodying these general principles. Thus Co Tui introduced the idea of supplying nitrogen metabolic needs and at the same time an adequate gastric buffer, by using amino acid preparations for continuous oral or tube feeding during certain acute phases of ulcer therapy. Theoretically this type of treatment is effective because it meets caloric and nitrogen requirements, and at the same time introduces into the stomach a satisfactory buffer medium to reduce gastric acidity. It has the further advantage of supplying food in small bulk. I believe its chief value is in those cases where there is temporary or permanent narrowing of the pyloric orifice, and where there is a consequent and important state of malnutrition with loss of body nitrogen. It is possible that its use is also indicated in the period after severe hemorrhage when nitrogen reserves must be made up efficiently and rapidly. For the average uncomplicated case it is an unnecessary refinement, which is somewhat more expensive than need be and which presents the patient with the difficulty of ingesting a fairly unpalatable mixture. Furthermore, recent studies have cast serious doubt upon its efficacy as a buffer substance. Another specialized dietary maneuver is the constant milk drip by nasal tube devised by Winkelstein. Its effectiveness depends on the constant introduction into the stomach of a solution containing calorific material, fats and protein. It undoubtedly acts as a buffer solution, and there can be little doubt that it will work. To my mind it possesses no *real* advantages over simple oral feeding, except possibly in very special circumstances, and the presence of a constant inlying nasal

Attempts to do more initially than simple closure of a perforated ulcer probably constitute bad surgical judgment.

The question of pyloric obstruction is somewhat less clear. When stenosis of sufficient degree has occurred, to preclude the handling of optimal quantities of food, then surgical intervention is an obvious necessity. About this there can be no argument. The difficulty that frequently arises derives from the definition of the word obstruction. Gastric stasis may occur secondary to an active ulcer in the gastric antrum, the pylorus or the duodenum. The appearance of obstructive signs and symptoms may be as great with no permanent stenosis as in those cases where fibrotic changes are marked. In the former instance they are due to spasm and edema secondary to an active ulcer and are usually amenable to intensive medical measures. In cases where important degrees of fibrous narrowing are present, medical measures are of no value except to aid in the proper timing and preparation for surgical procedures. For this the problem of obstruction, if handled first by a physician, should involve the use of several simple but rather rigid rules. No patient who is thought to be obstructed should be cared for by a medical man unless he at once sets definite limits to the period of what I would call therapeutic trial. The possibility of surgery should be at once recognized, and a tentative date for operation set. By so doing no valuable time is lost, and the measures proper for the treatment of partial and temporary obstruction will be fully effective in preparing the patient for surgery if such intervention is proved necessary. If the obstructive features have disappeared at the end of the allotted period, operation may be postponed or completely avoided as circumstances direct. Decisions should be the result of full coöperation between physician and surgeon, with full realization of the obligations of each in outlining treatment. Too frequently a partially obstructed patient is allowed to drift under medical therapy in the hope that the obstruction will slowly but steadily diminish. In such instances the usual result is a badly depleted patient who eventually is handed over to the surgeon in far from optimal condition. This patient is indeed a poor-risk subject, and the fault is entirely that of the medical man who does not recognize the importance of setting dates for critical decisions.

During the period of therapeutic trial in cases of obstruction, daily exact balances are absolutely essential. Initial blood chemistries deter-

mining blood electrolytes, serum protein values, nonprotein nitrogen, and possibly hematocrit figures and CO_2 levels must be combined with an accurate fluid balance chart. Too much stress cannot be placed on these fundamental measures. Measured gastric lavage at regular intervals, to determine the degree and trend of gastric stasis, must be consistent over a period of days. The type and quantity of oral feeding will obviously depend on the degree of stasis. Replacement of electrolytes, fluids, and calories in the form of dextrose and amino acid hydrolysates may be carried out quantitatively by intravenous administration. Plasma should not be used. The measures advocated by Co Tui may have a special bearing, to my mind, in this particular situation, and possibly may be used very effectively because of the low bulk, high buffer, high nitrogen values of the amino acid mixtures. In some instances the continuous milk drip might be equally effective, but only where the total bulk is not an important consideration. I might add that in many of these cases, where the obstruction is only temporary and secondary to an active ulcer, simpler measures with small frequent milk feedings, thorough atropinization and sedation are surprisingly effective. If under careful medical therapy gastric returns diminish, and replacement measures restore electrolyte, water and other deficits, then a decision against immediate surgery can readily be made after a proper interval. If progress is not favorable, as already mentioned, a decision for appropriate surgery can be made without loss of valuable time for preparation.

Repeated attacks simulating obstruction, or fully demonstrated stenosis, can be satisfactorily treated only by surgical measures. As a rule I feel sure that subtotal gastrectomy is the method of choice. There is an occasional poor-risk patient who may still be a candidate for posterior gastroenterostomy, but I believe this constitutes a very small number. The question of gastroenterostomy and vagotomy as a proper measure I shall discuss a little later. It is fair to say that the operative mortality following subtotal gastrectomy in properly prepared patients is extremely low when the operation is performed by adequately trained men. In the average case optimal results are obtained with about one week of careful preoperative preparation. In doubtful cases, a decision for or against surgery should be possible in this period of time.

The subject of hemorrhage is also somewhat controversial. Certainly the therapy of massive bleeding cannot be made a simple routine.

In general it can be said that the mortality figures from massive hemorrhage in patients under 45 are relatively very low, 1 to 2 per cent. In the later decades it is distinctly higher. Age alone does not supply the criterion that is to determine immediate or subsequent decision. The immediate problem in the treatment of massive bleeding is the treatment of shock. This can best be handled by the use of whole blood transfusions, given slowly, in sufficient quantity. Plasma should not be used. In older people, a low hemoglobin is less well tolerated than in younger individuals, and the hemoglobin probably is best raised to a level approaching 12 grams per cent. Rapid transfusions should be avoided unless rapid active bleeding is apparent, and then usually only as a preparation for emergency surgery. Sedation is generally indicated, but morphine as a rule is not the drug of choice because of the chance of increasing nausea and vomiting. Sodium luminal is often effective. Once shock is controlled, oral feeding should be initiated, using small, frequent feedings. The importance of this move was recognized many years ago by Andresen, forgotten, and rejuvenated by Meulengracht. The principle of providing a buffer medium, nitrogen and calories is still a fundamental one in this type of emergency. Just what type of food is to be chosen obviously is of little moment, except that it should be nonbulky, nonirritating, and capable at the same time of filling the above requirements. Andresen employed gelatin; Meulengracht used a fairly generous display of high protein foods, including meat. Co Tui has employed amino acid mixtures; Winkelstein a constant milk drip. All these measures work. My own experience leads me to believe that the more complicated measures are rarely necessary, although I am sure they may be indicated in an occasional instance. At the risk of being called reactionary, I still prefer simple frequent milk feedings in most cases, because of the simplicity of the method. I might add that I have tried the various measures that I have attempted to discuss. Antacids, I believe, offer little and are better avoided if adequate feeding can be obtained. Antispasmodics by injection, given at regular periods, probably are just as helpful, without adding to the difficulties of oral feeding. Once bleeding has stopped, as it usually will, the patient should be treated according to routine accepted methods, and an approach made to future decisions. Incidentally, iron by mouth is, I think, contraindicated in the immediate recovery period. It usually is quite unnecessary, there being a reasonable quantity of

storage iron available, and it may be irritating to the gastroduodenal mucosa. In most instances, a major hemorrhage should be an indication for elective subtotal gastrectomy. Individual exceptions to this rule do not alter the thesis that recurrent hemorrhages are to be expected. Certainly a second hemorrhage should force the decision. If hemorrhage does not cease, or recurs immediately, then in most instances a decision in favor of emergency surgery should be made if properly trained gastric surgeons are available. If they are not, the risk of surgery at this juncture is greater than the risk of continued medical treatment. In trained hands, supported by modern measures, subtotal gastrectomy may be properly advised. Such a decision is an individual one, however, and should be made as early as possible in critical cases. One maneuver should be mentioned. In patients with massive bleeding, where the source is not known, early x-ray examination, *without manipulation*, may define the problem immediately, without any appreciable added risk.

Possibly the most difficult problem is that of the intractable ulcer. Without discussing it in too great detail I should like to emphasize two points. Elective ulcer therapy has only a single aim,—the rehabilitation of the patient with the greatest protection of the patient from recurrences. If medical treatment cannot do this, regardless of the underlying reason, with few exceptions surgery should be performed. This is especially true because the risk of gastric surgery as an elective measure has been reduced to a figure of 1 to 2 per cent when the surgeon is well trained. In the presence of other serious disease, such as severe nephritis, advanced cardiac or pulmonary disease, obviously surgery may not be a proper move. One exception to choosing a surgical approach in this group of patients should be noted. A small number of ulcer patients do not respond to treatment because of a co-existing intractable neurosis. Otherwise proper operative measures will nearly always fail when applied to these patients. The ulcer may be controlled, but the patient is still a hopeless invalid, who has a new cause for further disability,—a major surgical procedure. Surgery should be avoided in these cases.

In the time remaining I wish to discuss two points,—ulcer surgery as such, and the problem of gastric ulcer.

The success of any elective operative procedure for chronic disease must be judged from several standpoints. Immediate mortality figures

are the first consideration. With special exceptions, the operative risk has been steadily reduced until in well-trained hands it is in the vicinity of 1 to 2 per cent. This is true of gastroenterostomy, subtotal gastrectomy, and vagotomy. The pertinent question, therefore, is one concerning the end-result. Evaluation of any form of ulcer surgery requires *many* years of careful follow-up, which should concern itself primarily with two points: 1) ulcer recurrence and 2) the general overall result of health or disability. It does little good to prevent ulcer recurrence if the patient is left an invalid.

In the case of simple gastroenterostomy, the experience of the last 30 years has convinced most of us that this operation does not prevent recurrent ulcer with sufficient surety to justify its use as a routine procedure. Although figures vary in different clinics, the general thoughtful consensus is that reactivation of duodenal ulcers, or the formation of stomal or jejunal ulcers, is altogether too frequent to warrant the use of gastroenterostomy in any but an occasional patient. Anastomatic ulcers probably result in at least 10-15 per cent of all cases that are carefully followed, although individual statistics range from 1 to 40 per cent. The experience with subtotal gastrectomy also varies, and precise follow-up figures are still to be awaited. Probably the most careful and critical follow-up is that from the Mount Sinai Hospital of this city. I imagine that further evaluation will reveal that in subtotal gastrectomy for duodenal ulcer, if the pyloric antrum has been completely removed, anastomatic ulcers may be expected in approximately 5 per cent of the cases. The complete removal of the pyloric antrum is, I believe, a measure that is essential for optimal results. In our experience at the Massachusetts General Hospital the incidence of stomal ulceration is very high in those instances where even a small portion of the antral end of the stomach remains. There are times when complete removal is technically very difficult because of the amount of inflammatory reaction in the neighborhood of an active ulcer, and in these instances experience has shown that a two-stage procedure may be of immense value, inasmuch as it enables the surgeon to carry out the actual resection of the pylorus and proximal duodenal area at his leisure after the acute inflammatory process has completely subsided. The incidence of recurrent ulcer following the procedure of vagotomy is not known, due to the fact that a critical follow-up on a sufficient number of cases is not available. Five years

at least, and preferably 10 years, must elapse before any adequate information is available. In our own series, in which a careful follow-up is being carried on by Moore, recurrences have been seen in approximately 5-6 per cent of the cases operated during the last 4 years. Obviously enough time has not yet elapsed. It can be said, however, that no surgical procedure has completely solved the problem, although such a statement in no way militates against the enthusiastic use of present surgical measures in properly chosen cases. One must insist, however, that following surgery the patient must still take reasonable care of himself, with special reference to regulated eating habits, the unwise use of alcohol, and the avoidance of prolonged serious nervous tensions.

The evaluation of operative therapy must go further. Even without ulcer recurrence, is the patient still bothered by annoying symptoms as a result of his operation? As regards subtotal gastrectomy, two facts are worthy of mention. The so-called "dumping syndrome," which follows this operation in from 10 to 15 per cent, occasionally becomes a major symptom and, because of its severity makes the patient as great an invalid as he was before surgical intervention. The exact mechanism of this phenomenon is not fully understood, but it probably involves motor and vasomotor disturbances occurring as the result of rapid jejunal filling in an over-reactive patient. It rarely occurs in stable individuals, and it may represent a true neurotic manifestation. Atropine in full doses before meals and frequent feedings of small bulk and low in sugars sometimes help. Although it frequently simulates a hypoglycemic reaction it is very improbable that a sudden reduction in blood sugar initiates the phenomenon. Fortunately it occurs as a major symptom in very few cases.

An equally or more important sequel of subtotal gastrectomy is that of faulty nutrition of sufficient degree to cause an important loss of weight with its accompanying loss of strength and endurance. I believe that such a result is to be found in about 15 per cent of cases. In approximately 85 per cent of cases there are no nutritional disturbances, and a satisfactory explanation of the occurrence in the 15 per cent of patients is not yet available. In all probability several factors are operative. Frequently these individuals have pronounced neurotic traits which influence their appetite and tolerance of food. I think nearly all of the patients are of the slender, over-active type, whose

daily metabolic requirements are augmented by constant muscular activity even when relatively inactive. Stool studies in carefully controlled experiments indicated increased loss of fats in the feces, with resulting loss of caloric material. Probably all these factors operate to make these patients serious medical problems, and to invalidate what otherwise would have been successful surgery.

A further word concerning vagotomy. This procedure is still too recent for complete evaluation. For proper appraisal it should be used only in unobstructed duodenal ulcers in patients who have been resistant to good medical therapy. Unless the procedure is thus limited no adequate judgment can be made of its particular contribution to ulcer therapy. If combined with gastroenterostomy, it may be a valuable procedure, but the combined operation precludes any final judgment on vagotomy. It should never be used for gastric ulcer. If performed, it must be followed with extreme care in order to fully study the final results. At least 3 to 4 years more are needed. It should be remembered that vagotomy in a sense represents a physiological procedure which aims at controlling gastric secretory and motor activity, rather than an operation which resects an important organ to remove gastric responses. The side-effects of vagotomy are fulness, heaviness after meals, diarrhea, and so forth, and are encountered as transient, mild phenomena in 15 to 20 per cent of cases. In somewhere between 5 and 10 per cent these disturbances may persist for months and may constitute major disabling symptoms. In the experience of Moore and myself they eventually subside. Those symptoms associated with poor gastric emptying can be successfully treated with urecholine, as proposed by Miller and his associates. The recurrences of duodenal ulcer that we have encountered have been easily handled, and usually followed very gross dietary or alcoholic irregularities. As one patient put it, the operation provided good armor-plate protection that could be penetrated if the shooting got heavy enough! At present Moore and I feel that the procedure should not be used for mass production, but only for a few carefully selected and carefully followed cases. This point is worthy of emphasis because to a good thoracic, or very well trained abdominal surgeon, it is a relatively simple and safe operation. One additional point is to be made. At present it represents by far the best method for the successful treatment of gastroduodenal ulcer.

A last point of discussion is the question of gastric ulcer. This controversial subject still needs clarification. I can merely present my own convictions. Despite the ease with which benign gastric ulcer can be controlled medically, I am firmly convinced that every patient with gastric ulcer warrants a consideration of surgical intervention because of the danger of unrecognizable cancer. No medical man has the right to decide in favor of medical treatment unless he is fully prepared to follow the patient closely and indefinitely. If there is doubt after careful x-ray or gastroscopic examination, if there is evidence of failure to heal after careful treatment, if there is histamine achlorhydria, if the ulcer is in other locations than the classical mid-lesser curvature, —surgery to my mind is mandatory and should involve adequate resection. Diagnostic errors may be further reduced by the study of gastroscopic biopsies, and by cytological means of gastric contents by the Papanicolaou method. I do not believe, as some do, that all gastric ulcers should be resected, but I am sure most of them should. One reason for so thinking is that even in the case of a benign ulcer, operative mortality is very low in good surgical hands and postoperative difficulties are minimal. Furthermore, the chance of diagnostic error in “doubtful” lesions is far from negligible. In a recent survey of the surgery of the last ten years at the Massachusetts General Hospital, Welch has shown that more than 10 per cent of the cancers of the stomach coming to operation were considered benign prior to surgical intervention. Only persistent, repeated, complete studies of gastric lesions by all diagnostic measures available will enable a physician to decide in favor of conservative measures in the treatment of benign gastric ulcer.

A further word as to the newer diagnostic procedures. Cytological studies of gastric washings, using the Papanicolaou technique, may provide further identification of doubtful lesions. In order to succeed, the material obtained by aspiration must be carefully collected, immediately spun at high speed, fixed and stained, and then examined by a microscopist who is very experienced in the method. In a recent series of patients so studied at the Massachusetts General Hospital by Ulfelder and Graham, 85 per cent positive diagnoses were made by this method. With further experience such a measure may help to differentiate benign from malignant lesions and may increase the number of early diagnoses. Similarly, carefully obtained gastroscopic biopsies may provide important diagnostic material in doubtful cases.

In a review of this very broad subject, I have attempted to point out the advantages and disadvantages, the indications and contraindications for various medical and surgical therapeutic measures that must be applied to the problem of ulcer. As a final comment, may I repeat what I hope I have implied,—namely, that favorable results can only be obtained by thorough and whole-hearted collaboration between physician and surgeon. Without this, ill-considered measures or half-hearted measures are employed and the results are totally inadequate for the patient afflicted with this chronic disease.

MODERN TREATMENT OF SYPHILIS, INCLUDING SYPHILIS OF THE CENTRAL NERVOUS SYSTEM*

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AT THE risk of carrying coals to Newcastle it seems advisable to consider certain important characteristics of syphilis before discussing its treatment. The early stages of the disease (primary and secondary syphilis) comprise a relatively benign, acute phase of the infection during which the body tissues react differently to the *Treponema pallidum* than during the late chronic phase. The early lesions of syphilis are infectious but non-destructive and self-limited. If early syphilis is not treated, within a maximum period of two years the infected individual develops a permanently altered reaction to the treponemes which comprises the late chronic phase of the disease. The late lesions are rarely self-limited and they are always destructive. Probably 60 per cent of untreated syphilitics never develop demonstrable late lesions during life and remain in the so-called latent stage. As is well known, however, it is impossible to determine in advance who will remain in the latent stage and who will develop demonstrable late lesions. Gummas and gummatous reactions may occur thirty years or more after infection.

If the early acute phase is untreated the infected individual, with rare exceptions, develops a permanent refractory state toward early lesions. In other words, whether cured or not two or more years after infection, reinfection with the *T. pallidum* may occur but it will not be followed by the appearance of early lesions. If, however, antisiphilic treatment is received during the early phase, the permanent establishment of the refractory state toward early lesions is inhibited, and unsuccessfully treated patients may relapse or successfully treated patients may be reinfected with the development of early lesions.

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Aided by grants from the United States Public Health Service.

^aThe immunologic differences between early and late syphilis are not confined to the establishment of a permanent refractory state toward early lesions. Positive serologic tests for syphilis (STS) can be reversed to negative by antisyphilitic treatment much more rapidly during the early than the late stages of the infection. Following successful treatment of early seropositive syphilis, quantitative STS show a rapid fall and in the majority of cases become negative within three to nine months, depending on how early in the course of the disease the patient is treated. Some individuals treated for early syphilis have low STS titers for more than nine months after treatment. Experience has proved that such patients do not represent failures of treatment and that they will finally become seronegative without further therapy unless relapse occurs in which case there is a sharp rise in the quantitative STS titers. The rapid drop of STS titers which occurs following therapy of early syphilis is rarely noted after treatment of late syphilis. In at least 75 per cent of late cases no therapy will reverse positive STS to negative within five years and some patients remain seropositive for life.

The above statements about the STS following treatment of early and late syphilis have long been valid but there are still differences of opinion and also misconceptions about the interpretation of persistent positive STS after treatment. In my opinion, the fact that STS remain positive for many years following treatment of late syphilis does not necessarily mean the persistence of a syphilitic infection. It is not within the scope of this paper to give reasons for this belief but it should be remembered that STS are not tests for the microorganisms of syphilis but for a globulin factor called reagin. All of the tests are based on the principle of identifying antibodies. Presumably reagin is an antibody but it is neither protective against syphilis nor is it absolutely specific for syphilis. Individuals vary greatly in the amount of reagin they are capable of forming and there is no relationship between the height of the STS titers and the severity of the disease. Following successful treatment of early syphilis positive STS, with occasional exceptions, become completely negative within two years, and the reversal of positive tests to negative is one of the proofs of cure of early syphilis. Following treatment of late syphilis, the failure of positive STS to become negative is in no way proof of the failure of treatment, and it is a serious mistake to treat late syphilis with the sole purpose of obtaining negative serologic tests.

More time might well be spent in clarifying the foregoing statements but the subject of this paper is the penicillin treatment of syphilis to which I now turn.

Difficulties in Evaluating Penicillin Therapy of Early Syphilis: No antisyphilitic agent has had such controlled studies of its therapeutic effectiveness as penicillin. But, in spite of carefully planned programs of therapy and record-keeping, the evaluation of penicillin therapy of syphilis has been handicapped by a number of uncontrollable variables. Both the quality and kind of penicillin preparations used during the past five years have changed so rapidly that the prolonged follow-up research needed to evaluate various schedules of treatment has been unable to keep pace with changes in the penicillin products. Of even more importance all statistics on the rapid treatment of early syphilis have been vitiated by the occurrence of many probable reinfections. The greater the reservoir of infectious syphilis the greater is the possibility of reinfection. In numerous communities where the most careful follow-up observations on treated patients have been recorded, the reservoir of infectious syphilis has altered significantly during the past five years.

Because the incidence of infectious syphilis in New York has declined notably within the past two years and because penicillin G does not vary in its therapeutic effectiveness to the same extent as the earlier amorphous penicillin, statistics recording the results of treatment of early syphilis during the past two years probably give a truer picture of the effectiveness of therapy than do those reported for the previous three years.

Variations in Penicillin Preparations: The original penicillin preparations used in the treatment of syphilis were all sodium, potassium or calcium salts of amorphous penicillin which were dissolved in water and injected at frequent intervals. In 1945 calcium salts of amorphous penicillin were mixed with oil and beeswax thus delaying absorption. By 1946 amorphous penicillin began to be replaced by crystalline penicillin G which is now used almost exclusively. Early in 1948 sodium or calcium penicillin G in oil and wax was replaced by the relatively insoluble procaine salt and a few months later procaine penicillin G in oil and 2 per cent aluminum monostearate became available for general use.

As is well known, aqueous solutions of very soluble salts of penicillin

are rapidly absorbed and excreted. To obtain continuous demonstrable blood concentrations of penicillin with doses of 20,000 to 80,000 units in aqueous solution, injections must be given every three or four hours. POB preparations were more slowly absorbed than aqueous solutions. Hewitt, Whittlesey and Keefer¹ found that the maximum blood concentration of penicillin after an injection of 300,000 units of crystalline sodium penicillin G in oil and wax occurred about 4 hours after the injection and in some cases levels of 5 units per cc. were found in the blood. Demonstrable blood concentrations of penicillin after an injection of 300,000 units of POB could be found for fifteen to thirty hours.

Following an injection of 300,000 units of procaine penicillin G in oil or water, Hewitt, Whittlesey and Keefer¹ found demonstrable blood concentrations twelve hours after administration in 100 per cent of cases and twenty-four hours after injection in 92 per cent. The maximum concentrations occurred about four hours after injection and varied from 0.08 to 2.5 units per cc. of serum.

Following an injection of 300,000 units of procaine penicillin (small size particles) in oil and 2 per cent aluminum monostearate, the relatively high blood concentrations of penicillin obtained with the more rapidly absorbed products do not occur but demonstrable blood levels of 0.03 units or more were found in 90 per cent of 173 cases for four or more days.²

Up to the present there is little evidence that brief high blood concentrations of penicillin are needed in the treatment of syphilis. The time during which penicillin is active in the body tissues, however, is of great significance in antisyphilitic therapy. Consequently the new very slowly absorbed penicillin preparations may well prove of great value in antisyphilitic therapy. Daily injections of these preparations are probably unnecessary. Thus the physician now has at his disposal a variety of penicillin products by means of which he can choose schedules of antisyphilitic therapy which will meet his own convenience and that of the patient. It should be recognized, however, that insufficient time has passed for the evaluation of treatment with procaine penicillin G in oil and aluminum monostearate. The data now available on the treatment of syphilis with penicillin consist entirely of follow-up studies of patients treated with aqueous solutions of penicillin and POB. The chief value of the data on treatment schedules with the earlier penicillin preparations is that they furnish us with a background for determining

the optimum total dosage of penicillin and the optimum time of therapy.

Treatment of Early Syphilis With Aqueous Solutions of Penicillin and POB in Eight Days: The earliest schedules of penicillin therapy assigned to us at Bellevue Hospital by the Syphilis Study Section of the Subcommittee for Venereal Diseases of the National Research Council called for such small total doses over an eight-day period that they can now be disregarded. From the early experience we learned that for an eight-day period of therapy total doses of less than 2,400,000 units of penicillin in aqueous solution or in oil and wax were unsatisfactory. At Bellevue Hospital after treating fairly large series of patients with total doses of only 600,000 to 1,200,000 units of penicillin in seven and a half days, a variety of treatment schedules using more adequate doses were used.

Table I shows the cumulative "failure" rates for seven treatment schedules, the time of therapy in all cases having been seven and a half to eight days.

Although the number of patients with early syphilis treated by each of the schedules is relatively large, when each series is broken down into four different categories, the numbers of patients treated for seronegative primary syphilis and of those treated for relapse or reinfection following previous therapy of early syphilis are too small for significant statistical analysis. Nevertheless, it is of interest to note the percentages of so-called failures in each four categories, if for no other reason than to observe the fallacy of accepting statistics at face value without taking every possible variable into consideration.

Cumulative "failure" rates are computed by a rather involved statistical analysis based on the number of patients actually followed up for varying periods of time and not on the number treated. "Failures" include all those who relapsed, were reinfected or were re-treated because of persistently high STS titers. Since the number of patients kept under observation usually declines over a period of years and since all patients requiring re-treatment are included as failures, regardless of when they were re-treated, it is obvious that the longer the period of follow-up, the higher the cumulative "failure" rates become. If as many as 40 per cent of the treated patients are lost within the first year after treatment, it is unlikely that cumulative "failure" rates give an accurate estimate of the failures among those who were not followed up. The fault does not lie with the method of computing "failure" rates but with the diffi-

TABLE I

	Seronegative Primary					Seropositive Primary					Secondary					Retreatments of Infectious Relapses or Reinfections				
	Months of Follow-up	Number Treated	Number of Observed Failures	Cumulative Failure Rate*	Number Treated	Number of Observed Failures	Cumulative Failure Rate	Number Treated	Number of Observed Failures	Cumulative Failure Rate	Number Treated	Number of Observed Failures	Cumulative Failure Rate	Number Treated	Number of Observed Failures	Cumulative Failure Rate				
1146 Patients Treated with 1,200,000 U. Penicillin (20,000 u. q. 3 hrs. for 60 doses) and 0.32 gms. Ma- pharsen. (Nov. 1944 to Dec. 1945)	36	91	15	20.9	214	38	26.9	743	153	33.1	98	21	38.4							
807 Patients Treated with 600,000 U. Penicillin in Beeswax and Oil Daily for 8 days. (Aug. 1945 to July 1946)	24	62	5	9.0	182	25	18.3	455	72	25.0	108	15	19.2							
236 Patients Treated with 2,400,000 U. Penicillin (40,000 u. q. 3 hrs. for 60 doses), 0.32 gms. Maphar- sen and 5 Bismuths. (Mar. 1946 to July 1946)	21	20	1	1.3	64	5	9.1	137	21	21.4	15	0	0							
256 Patients Treated with 2,400,000 U. Penicillin G (40,000 u. q. 3 hrs. for 60 doses). (July 1946 to June 1947)	17	32	1	3.2	47	4	9.9	167	18	15.7	10	0	0							
251 Patients Treated with 2,400,000 U. Penicillin G (26,666 u. q. 2 hrs. for 90 doses). (July 1946 to June 1947)	17	23	3	18.4	60	6	14.7	154	14	18.3	14	1	25.0							
223 Patients Treated with 4,800,000 U. Penicillin G (80,000 u. q. 3 hrs. for 60 doses). (July 1946 to June 1947)	17	14	0	0	26	4	22.3	97	12	18.9	86	12	18.8							
228 Patients Treated with 4,800,000 U. Penicillin G (53,333 u. q. 2 hrs. for 90 doses). (July 1946 to June 1947)	17	14	0	0	37	4	11.4	97	8	12.3	82	8	13.4							

* Cumulative failure rates are based on number of patients kept under observation and not on the number treated.

culty of keeping large numbers of patients who do not feel sick under observation for long periods. At Bellevue Hospital we have succeeded in keeping over 60 per cent of the patients treated on a research basis under observation for at least two years. Nevertheless, our statistics as well as those of most others who have reported on the long-term follow-up of patients treated for early syphilis are at best rough approximations of the true picture, and they fail to take into account the probable varying percentage of reinfection in different series of patients.

Table I shows cumulative "failure" rates for different schedules of therapy used at different times and consequently the periods of follow-up after treatment vary. To compare the first series in Table I with the last four series we should know the percentages of "failures" following a seventeen-months period of observation. The cumulative "failure" rates for the first series at the end of a seventeen-months period of follow-up were as follows: seronegative primary syphilis, 14.6 per cent; seropositive primary syphilis, 20.4 per cent; secondary syphilis, 24.4 per cent; re-treated patients, 18.8 per cent.

In spite of variations in the "failure" rates of the 7 different treatment schedules shown in Table I the differences are not statistically significant. If the numbers of patients in all four categories in each series are totaled, the cumulative "failure" rates for the various treatment schedules of early syphilis are about 20 per cent. Attention might well be called to the higher percentage of "failures" in the series treated with 80,000 units of penicillin G every three hours for 60 doses than in the series treated with only half that amount of penicillin at the same intervals. In my opinion the only way this appreciable, though not statistically significant, difference can be explained is by the higher incidence of reinfections in the group treated with 4,800,000 units than in the one treated with 2,400,000 units. Evidence for my belief that many of the so-called failures were actually reinfections is available but time does not permit such detailed analysis in this report. In previous publications I have considered the differentiation between relapse and reinfection.^{3, 4}

From the statistics shown in Table I we can conclude: 1) treatment with 2,400,000 units of penicillin in aqueous solution (with individual injections every two to three hours) is as effective as when twice that amount of penicillin is used; 2) the addition of 0.04 gm. arsenoxide to a total dose of 1,200,000 units of penicillin in aqueous solution gives no

better results than 2,400,000 units of penicillin alone; 3) daily injections of 300,000 to 600,000 units of POB are as effective as 40,000 to 80,000 units of penicillin in aqueous solution injected at three hour intervals.

"Failure" rates of 20 per cent are far from satisfactory but in all probability the actual results were much better than the statistics indicate because no attempt was made to differentiate relapses from reinfections.

Treatment of Early Syphilis With POB in Fifteen Days: It was not until October 1947 that we extended the period of penicillin therapy for early syphilis at Bellevue Hospital from 8 to 15 days. The treatment schedule consisted of 15 daily injections of 600,000 units of POB. By the time this schedule was in use the number of early syphilis cases admitted to our service had declined from a high of over 250 a month in previous years to less than 75 per month. For a variety of reasons all of the patients treated for early syphilis were not placed on a research basis. Since October, 1947 we have observed for 8 to 15 months 134 patients treated for dark field positive early syphilis with 600,000 units of POB for 15 days. Of these 3 were re-treated because of new infections, each of the 3 having developed new chancres at different sites from their original primary lesions; 1 was re-treated because of a persistently high quantitative Kahn test 9 months after therapy and another patient will be re-treated for the same reason. It has been our practice to re-treat patients who have positive STS in serum dilutions of one to eight or more nine months after treatment.

I am by no means certain that the excellent results obtained so far with the fifteen-day schedule of therapy can be attributed entirely to the increased total dose of penicillin and to the prolongation of therapy. For reasons which I cannot take the time to give here I am convinced that we had a much lower incidence of reinfections in the more recent series than in any of those in Table I. It is also probable that as good results could have been obtained with daily injections of 300,000 units of POB as with 600,000 units because reports from other clinics have shown excellent results with daily injections of 300,000 units for fourteen to sixteen days.⁵ But, in spite of my doubts concerning the comparative value of the various schedules of therapy for early syphilis on which we now have data, it now seems that the optimum period of penicillin therapy for early syphilis is about fifteen days.

As yet we have inadequate data on the use of procaine salts of penicillin in the treatment of early syphilis. There is every reason to believe, however, that procaine penicillin G in oil or water without aluminum monostearate is comparable in therapeutic effectiveness to POB. Procaine penicillin G in oil and aluminum monostearate, on the other hand, offers possibilities of very different time-dose relationships in the treatment of syphilis than either POB or procaine penicillin without aluminum monostearate. At present in coöperation with the Syphilis Study Section of the National Institute of Health three different schedules of therapy with procaine penicillin G in oil and aluminum monostearate are being used at Bellevue Hospital: 1) A single injection of 1,200,000 units. 2) An injection of 1,200,000 units once a week for two weeks. 3) An injection of 1,200,000 units once a week for four weeks.

Another year will be needed before the results of the above treatment schedules can be evaluated. Obviously they represent an important simplification of the treatment of early syphilis if they prove successful.

Treatment of Relapsing Early Syphilis: Following treatment of early syphilis patients may relapse with or without early infectious lesions. In the latter case the relapse is determined only by marked sustained rises in quantitative STS from previous levels (serologic relapse). Relapses and also reinfections may occur before or after the STS have become negative.

Referring again to Table I it will be seen that the cumulative "failure" rates of patients treated with at least 2,400,000 units of penicillin in eight days because of relapse or reinfection were similar to those of patients treated with the same amount of penicillin for original infections. Many of the patients re-treated were probably reinfected but unquestionably some patients with early syphilis require more prolonged treatment and possibly greater amounts of penicillin than others. So far on our service we have not found a single case of early syphilis that failed to respond to penicillin or failed to have a successful outcome of treatment provided relapses were re-treated with increased doses over a period of at least 15 days. An example of the results following re-treatment of repeated relapses after inadequate therapy is shown in Table II.

I do not advise that relapses of early syphilis be re-treated as shown

TABLE II

J. L., a white female 26 years of age, was admitted to Bellevue Hospital April 15, 1944 with darkfield positive secondary syphilis. She was first treated with 10,000 units of penicillin in aqueous solution every three hours for sixty doses. The reports of her quantitative STS at the time of and following treatment were as follows:

<i>Serologic Tests</i>					
<i>Date</i>	<i>Comp. Fix. Titers</i>	<i>Quantitative Kahn Tests</i>	<i>Date</i>	<i>Comp. Fix. Titers</i>	<i>Quantitative Kahn Tests</i>
4-17-44	130	256	5-31-44	12	8
5- 3-44	47	64	6- 8-44	8	Not done
5-12-44	36	16	6-15-44	12	16
5-18-44	12	8	6-22-44	75	32
5-25-44	9	8	6-29-44	110	128

On 6-22-44 and 6-29-44 no lesions were found but a spinal fluid examination showed pleocytosis with 84/3 cells and a 1+ Wassermann test in .25 cc. of spinal fluid. She was retreated, 7-7-44 to 7-14-44, with 40,000 units penicillin in aqueous solution every six hours for thirty doses.

<i>Serologic Tests</i>					
<i>Date</i>	<i>Comp. Fix. Titers</i>	<i>Quantitative Kahn Tests</i>	<i>Date</i>	<i>Comp. Fix. Titers</i>	<i>Quantitative Kahn Tests</i>
7- 7-44	160	128	10- 5-44	Not done	128
8-10-44	36	32	10-23-44	Not done	256
9- 7-44	36	16	10-24-44	120	Not done

No lesions were found at the time of her second serologic relapse. The spinal fluid complement fixation titer was 15; cells 160/3; total protein 26; colloidal gold test added to 94. She was retreated 10-23-44 to 10-30-44, with 40,000 units penicillin in aqueous solution every three hours for sixty doses and 0.3 gm. mapharsen (5 x .06).

<i>Serologic Tests</i>					
<i>Date</i>	<i>Comp. Fix. Titers</i>	<i>Quantitative Kahn Tests</i>	<i>Date</i>	<i>Comp. Fix. Titers</i>	<i>Quantitative Kahn Tests</i>
10-23-44	120	256	1- 4-45	Not done	16
11-22-44	Not done	32	1-11-45	Not done	8
11-30-44	Not done	32	1-28-45	Not done	16
12- 7-44	Not done	16	2- 1-45	Not done	32
12-14-44	Not done	16	2-15-45	96	128
12-21-44	Not done	8			

On 3-5-45 a single darkfield positive papule was found on the right labium major and solitary papules were found on the left forearm and back respectively. Her spinal fluid tests on 3-6-45 were: Wassermann negative; cells 173/3; total protein 27; colloidal gold not done. She was retreated 3-15-45 to 3-20-45 with 50,000 units penicillin in aqueous solution every two hours for 180 doses—total 9 million units.

(TABLE II—continued on next page)

(TABLE II—continued)

<i>Serologic Tests</i>					
<i>Date</i>	<i>Comp. Fix. Titers</i>	<i>Quantitative Kahn Tests</i>	<i>Date</i>	<i>Comp. Fix. Titers</i>	<i>Quantitative Kahn Tests</i>
3- 5-45	120	256	10-11-45	3	3
3-20-45	82	128	11- 1-45	4	3
4-14-45	Not done	64	11-29-45	0	3
5- 8-45	Not done	64	12-17-45	2	3
5-17-45	14	32	1-16-46	Not done	3
5-25-45	Not done	32	2-27-46	Not done	3
6- 7-45	10	16	4- 3-46	Not done	1
6-14-45	10	16	6- 4-46	Not done	2
6-21-45	Not done	16	7-17-46	Not done	0
6-28-45	6	8	8-26-46	Not done	0
7-12-45	6	8	9-23-46	Not done	1
7-19-45	Not done	8	11- 8-46	Not done	0
8- 2-45	6	8	3-13-47	Not done	0
8-23-45	6	3	7-24-47	Not done	0
9-13-45	4	3	11-20-47	0	0
9-27-45	5	3	5- 4-48	0	0

The spinal fluid examinations on 8-2-45 and 9-23-46 were completely normal.

in Table II. A better plan is to re-treat a genuine relapse with from 6,000,000 to 9,000,000 units of penicillin over a period of at least two weeks. I see no reason why either bismuth or arsenicals should be used in the treatment of relapse unless a second treatment with penicillin fails or the original infection fails to respond to penicillin.

Treatment of Neurosyphilis With Penicillin: Early syphilis of the central nervous system, as a rule, responds readily to any type of good antisyphilitic therapy. But permanent arrest of late neurosyphilis is achieved in less than 50 per cent of cases treated with heavy metals and arsenicals. Prior to the advent of penicillin, fever therapy was the treatment of choice for all cases of late neurosyphilis. Yet, in spite of its recognized effectiveness, relatively few patients with neurosyphilis actually received fever therapy unless they had general paresis. Because of the difficulties in obtaining fever therapy many neurosyphilitics continued to be treated on an ambulatory basis with potentially toxic drugs for years. From 1939 to 1944 every patient with active neurosyphilis

admitted to our service at Bellevue Hospital received fever therapy, most of them having been treated with malaria. We now have several hundred patients who have been followed up for five or more years after fever therapy. Since April, 1944 we have used penicillin exclusively for the treatment of all types of neurosyphilis, and we have found penicillin more effective than malaria therapy.

In evaluating the results of therapy for neurosyphilis we have used the spinal fluid examinations as the only reliable guide to the arrest of the syphilitic process.^{6, 7, 8} Dartner, who was associated with Wagner-Jauregg when malaria therapy for general paresis was first used, has long believed that the best evidence of activity of a syphilitic infection in the central nervous system is the presence of increased cells in the spinal fluid. In active late neurosyphilis the pleocytosis is usually associated with increased total protein. Following successful therapy, the cells in the spinal fluid should be less than 4 per cu. mm. three to four months after treatment, and increased protein determinations should show a definite decrease. Over a prolonged period of observation, quantitative Wassermann reactions of the spinal fluid, increased total protein values and quantitative colloidal gold tests should show a gradual but continuous trend toward normal. More than five years may pass before the Wassermann reaction of the spinal fluid becomes completely normal after successful treatment. In our experience, following treatment of neurosyphilis, if the cells were normal and the other tests showed a definite trend toward normal values, re-treatment with either fever therapy or penicillin failed to hasten the reversal of abnormal spinal fluid tests to normal. Furthermore we have not found that additional antisyphilitic treatment improved the clinical symptoms and signs of patients whose spinal fluid tests showed no evidences of an active syphilitic inflammation in the central nervous system.

The spinal fluid tests are of such great importance in the management of neurosyphilis that every effort should be made to ensure accurate and careful laboratory tests. We have found that the best spinal fluid complement fixation tests for syphilis and the most satisfactory colloidal gold tests have been furnished by the New York State Department of Health laboratories.^{9, 10} The New York State laboratories titer the spinal fluid complement fixation tests for syphilis in units in the same way that complement fixation tests of the blood are titered. They also do the new Lange colloidal gold test which gives

TABLE III—PENICILLIN SUCCESS AFTER MALARIA FAILURE

F.J.E. 50 W.M. General Paresis

Age 40—Three Years Routine Treatment

<i>Test No.</i>	<i>Date</i>	<i>Blood Wass.</i>	<i>S.F. Wass.</i>	<i>Colloidal Gold</i>	<i>T.P.</i>	<i>Pandy</i>	<i>Cells</i>
1	7-16-42	4+	4+	5555**	55	4+	140/3
AUGUST 1943—TERTIAN MALARIA (5), TYPHOID (3) and MAPHARSEN (10)							
2	11-30-43	4+	4+	2211**	85	4+	800/3
JANUARY 1944—20 PENTAVALENT ARSENICALS							
3	3-16-44	4+	4+	5554**	62	3+	70/3
APRIL 1944—20 ADDITIONAL PENTAVALENT ARSENICALS							
4	5-22-44	4+	4+	No data	60	2+	26/3
5	10- 4-44	4+	4+	No data	62	2+	250/3
OCTOBER 1944—4 MILLION UNITS PENICILLIN							
6	10-20-44	4+	150*	164***	46	2+	43/3
7	11-20-44	76*	110	154	47	1+	36/3
8	1-15-45	44	71	144	37	F.T.	9/3
9	4-10-45	39	80	122	37	V.F.T.	14/3
10	7-11-45	20	77	130	38	V.F.T.	3/3
11	10-29-45	21	70	133	34	V.F.T.	6/3
12	1-18-46	17	41	68	33	V.F.T.	6/3
13	7- 5-46	11	34	72	32	V.F.T.	3/3
14	10-25-46	10	37	79	28	V.F.T.	6/3
15	5-16-47	10	28	75	27	±	8/3
16	11-28-47	5	17	71	29	±	8/3
17	5-28-48	7	15	80	35	V.F.T.	6/3

* Titered in units.

** Readings of first four tubes by the older Lange method of colloidal gold test.

*** The figures given represent the sum of readings in all 10 tubes by new Lange method.

more constant readings than the old test and affords quantitative values by adding the figures for the reactions in all 10 tubes. I cannot take the time here to describe the new techniques of spinal fluid tests but I would stress the fact that in many hospitals and laboratories the techniques now used are outmoded and unreliable. Intelligent evaluation of treatment for neurosyphilis would be promoted, in my opinion, if the New York State laboratory techniques were widely adopted.

The spinal fluid tests are a much better guide to the effectiveness of treatment for neurosyphilis than are the clinical signs and symptoms.

The clinical response to treatment depends largely on the site and degree of permanent damage in the central nervous system. If important functioning parenchyma has been replaced by scar tissue it is manifestly impossible to restore normal function by antisyphilitic therapy.

There are still differences of opinion regarding the relative merits of malaria therapy and penicillin in the treatment of neurosyphilis, especially general paresis.¹¹⁻¹⁸ At Bellevue Hospital we are convinced that penicillin has caused clinical improvement similar to that obtained by fever therapy and we do not advise malaria or any other type of fever therapy unless penicillin treatment fails to produce satisfactory changes in the spinal fluid tests. Table III shows the spinal fluid findings in a general paretic who failed to have satisfactory response of the spinal fluid tests after malaria therapy but responded well to penicillin.

Of 376 patients treated for active neurosyphilis with penicillin alone and followed up for nine to fifty-four months, forty-three patients only were re-treated; thirty-two (8.5 per cent) having been re-treated because of relapse as shown by spinal fluid tests and eleven (3 per cent) having been re-treated because of an attempt to improve the clinical status of the patient, in spite of satisfactory findings in the spinal fluid. The dosage of penicillin varied from 2 to 9 million units and the duration of therapy varied from ten to nineteen days. The majority of relapses occurred in patients who received less than six million units over a period of less than fifteen days. When aqueous solutions of very soluble salts of penicillin were used, treatment with 40,000 units every three hours for 150 doses proved sufficient for most cases of neurosyphilis. Equally good results were obtained with daily injections of 600,000 units of POB for fifteen days. We are now treating neurosyphilis with 10 daily injections of 600,000 units of procaine penicillin G in oil and aluminum monostearate. With this treatment demonstrable blood concentrations of penicillin are found for five to seven days after the completion of therapy but we have no data as yet on a prolonged follow-up of any of these patients.

Treatment of Late Syphilis Other Than Neurosyphilis: Gummas and gummatous infiltrations have responded well to penicillin therapy at Bellevue Hospital and also in the experience of others except for 2 gummas, reported separately, which failed to heal after penicillin but responded to malaria therapy in one case and to mapharsen in the other.^{19, 20}

The evaluation of therapy for late latent syphilis and cardiovascular syphilis is difficult because in most cases positive STS do not become negative for years after treatment and no antisyphilitic therapy can restore normal function to an already damaged aorta or heart. In the case of latent syphilis quantitative STS obtained at regular intervals after treatment will usually show a gradual trend toward normal values although fluctuations in titers are not unusual. Re-treatment is not advised unless the quantitative STS show marked, sustained rises in titers from previous levels.

All types of late syphilis can usually be treated successfully with from 4 to 9 million units of penicillin given over a period of two to three weeks. The data now available indicate that such therapy has accomplished as much as or more than two years of routine therapy with heavy metals and arsenicals.

CONCLUSIONS

Although penicillin is not a panacea for every case of syphilis it has proved superior to all other forms of antisyphilitic therapy both in safety and therapeutic effectiveness. An occasional case may require therapy with arsenicals or fever but in general 4 to 9 million units of penicillin given over a 15-day period will accomplish as much in the treatment of all types of syphilis as any other known therapy.

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THE RISE AND PROGRESS OF MEDICAL EDUCATION
IN SCOTLAND*

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It is interesting to trace the spread of medical knowledge down the centuries, in space as well as in time, in geography as well as in history.

The progress led from Greece to Rome, then to the Moslem Empire; back again to Europe by way of Salerno, thence to Padua, Paris, and Leyden, and at last to Britain and America. As the centuries unfolded, the centre of medical education shifted from place to place, each new seat of learning contributing its quota to the accumulating mass of information. Scotland played a noteworthy part in this geographical march of medicine, and the story of Scottish Medicine since the beginning of the 18th century has often been told and is well known to most of you. Nevertheless the contribution of Scotland, prior to that time, is a less familiar, though no less important, chapter of medical history and for that reason it has been chosen as a subject which may be of some interest to the present distinguished company.

Medical Education has been, and may still be, regarded as one of the major activities of Scotland. Just as the Scottish marine engineer is to be found on all the Seven Seas, so has the Scottish medical man exercised his art in all quarters of the globe.

Of course, the story of systematic medical education in Scotland does not lead us back very far. The "qualified" medical man is a comparatively recent product; indeed, before the 16th century, the career of medicine was open to all who cared, or dared, to embark upon it, and even after regulations were framed, the standard of medical efficiency remained very uneven. After all,

we must remember that the General Medical Council, which controls the practice of medicine in Britain, came into being less than a century ago. Before 1858 there was no Register of "duly qualified" practitioners of medicine.

As a background to the story of the beginnings of medical education, let me try to sketch the history of medical practice in Scotland from the earliest times.

We have very little information regarding primitive medicine among the ancient inhabitants of Scotland. There may have been a special class of Medicine Men during the Stone Age. Certainly some such persons had their place during the Bronze Age, if one may judge from such scanty evidence as is furnished by a trephined skull of that period. The healing art was probably in the hands of a priestly class, the Druids, as they were called. Medicine and Religion have always been closely interwoven among primitive races, and the earliest hospitals of which we have any record were the pagan temples of ancient Greece.

The medical practice of those ancient Scots, or Picts, as they were called, was influenced by various early invaders. The Roman Army possessed medical officers, and certain surgical instruments, similar to those of Pompeii, as well as memorial tablets, found in Scotland, are relics of the presence there of Roman military surgeons. Another influence, of considerably later date, was that of Saxon doctors or "leeches." In one of the oldest Saxon manuscripts, the Leech Book of Bald, dating from the 10th century, there is mention of a number of Scottish herbal remedies.

Early in the Christian era, a knowledge of medicine was fostered by some of the Saints, notably by St. Columba (563 A.D.—

* An Address delivered to The New York Academy of Medicine, Section on Historical and Cultural Medicine, on April 19, 1949.

Iona) who had a hospital and a herb garden on the Island of Iona, and by St. Cuthbert (635-687 A.D.) who wrought wonderful cures in the South of Scotland and Northumbria during the 7th century. Doubtless those monks handed on to their disciples such knowledge as they possessed, because the care of the sick and wounded formed an important part of their duties.

In still later times, indeed as late as the 16th century, medical practice was a hereditary accomplishment handed down from generation to generation in certain families in the Western Isles of Scotland, notably in Islay and in Skye where the Macbeths and the McConachers were the accredited medical practitioners. They possessed manuscripts of the medical classics (Hippocrates, Galen, Avicenna, etc.) translated into the Gaelic tongue, some of which are preserved in the National Library of Scotland, in Edinburgh. Certain wandering scholars added to the medical knowledge of Scotland, such as Michael Scot (1175-1232) who, in the 12th century, studied and taught in the famous medical school of Salerno, and who brought back to his native country the current learning of the time, albeit interlarded with much magic and astrology.

Despite those praiseworthy efforts, there can be little doubt that in those early times the status of medicine was very low. In his *History of Scotland*, Tytler remarks that during the 13th century "the patient who fell into the hands of those feudal practitioners must have rather been an object of pity than of hope . . . it is probable that a sick or wounded knight had a better chance of recovery from the treatment of the gentle dames and aged crones in the castles whose knowledge of simples was great, than from the ministrations inflicted upon him by the accredited leeches of the times." Such was the condition of medicine in Scotland before the foundation of the universities and the establishment of systematic medical teaching.

Although their several histories overlap to some extent, it may best serve the purpose of the present lecture if one describes, each in its sequence, the rise and progress of medical education in the four Scottish

centres of learning.

St. Andrews, 1411

The first Scottish university was founded in 1411, at St. Andrews, the ecclesiastical capital and a place of great importance. Although provision was made, in the original charter, for a Faculty of Medicine, there appears to have been little teaching of medicine until the 18th century. Medicine was merely one subject of the Arts course, and like Anatomy, was merely a part of that modicum of general knowledge regarded as essential to every well-educated man.

The most famous Scottish medical man of the 15th century was William Scherez (1428-97). A native of St. Andrews, he had studied at Louvain, and so distinguished himself that on his return he became physician to King James III at a salary of "200 per annum, a velvet gown and oats for two horses." Eventually, he became Primate of Scotland, in succession to Archbishop Graham whose career of self-seeking and mismanagement ended in his loss of reason, and who was treated, or virtually imprisoned, in Loch Leven Castle under the medical supervision of Scherez, a difficult position for Scherez, yet his tact and skill were equal to it. Scherez bequeathed his excellent library to St. Andrews University; many valuable incunabula there bear his signature.

Within the next 150 years, the three colleges of St. Salvator (1450), St. Leonard (1572) and St. Mary (1587), were founded at St. Andrews, as also were the Universities in Glasgow and Aberdeen, but there was little or no teaching in Medicine in Scotland until after the Reformation; then John Knox laid down, in his *Book of Discipline of 1560*, that Glasgow should teach only Arts; Aberdeen, Law and Divinity; while St. Andrews was to be the Medical School for Scotland. This plan was never put into effect, and the only result was that St. Andrews continued for many a year to exercise the privilege of granting, or perhaps one should say, of selling, the degree of M.D.

Among those who took advantage of this arrangement during the 18th century were Jean Paul Marat and Edward Jenner. In 1772, the Duke of Chandos offered to St.

Andrews a sum of money to endow a chair of "eloquence." The University decided that a chair of medicine might prove more useful, and Thomas Simson was appointed. Simson and his early successors did little to adorn the chair, but the 5th Chandos professor, John Reid (1809-49), who was appointed in 1841, was a man of high attainment, whose death at the age of 40 was a great loss. Another distinguished Chandos professor, after the chair had become one of Physiology, was James Bell Pettigrew (1834-1908), whose studies of motion in animals and especially of the flight of birds, was of importance in the development of aeronautics.

Other new chairs were now created, and a Medical School was gradually evolved at St. Andrews University; although it did not become fully established until in 1897 it joined forces with University College, Dundee, which had been established in 1881.

ABERDEEN, 1494

And now let us turn northward to Aberdeen, the third of the Scottish Universities to be founded, but the first to institute regular medical teaching at a time when there was no other organized medical school in Britain. Aberdeen may thus claim to be "the Cradle of British Medicine." One of St. Columba's disciples, St. Machar, was sent on a northward journey, with instructions to build a church at a spot where a river took the form of a Bishop's Crook. The river was the Don, which assumes this sinuous course near its mouth, and the church became St. Machar's Cathedral, destined to be more securely founded by Bishop Dunbar some centuries later. Bishop Dunbar, in 1532, was also the founder of a hospital which, however, was rather of the nature of a home for pensioners than an institution for the sick or injured.

In the 14th century, Aberdeen was a centre of learning which produced the first Scottish historian, John of Fordun (*Scotichronicon*), and the first Scottish poet, John Barbour (*The Bruce*). The medical practice of that time, as already noted, was largely in the hands of "skilly women," or of landowners or lairds who attended to the health of their retainers. It was in

1494 that Bishop Elphinstone secured the coöperation of King James IV of Scotland to establish the University of St. Mary's, which became King's College, in Old Aberdeen. King James, it may be mentioned, took a keen interest in science and medicine. He conducted many experiments in his laboratory at Stirling, and it is on record that he actually paid several of his subjects for the privilege of extracting their teeth.

William Elphinstone, when he became Bishop of Aberdeen in 1483, found that part of Scotland "unlettered, ignorant, and almost barbarian." As the first Principal, or President, he chose Hector Boece, or Boyis, who had studied in Paris, and who wrote a history of Scotland. The Universities of St. Andrews and Glasgow had already been founded by Bishops, and Elphinstone improved upon those efforts. His University was not to be a mere sanctuary for scholars but a real centre of culture for the north of Scotland. From the very start, provision was made for the teaching of medicine by the appointment of a "Mediciner" at a salary of £12 a year with the right of salmon fishing in the River Don, a valuable perquisite. The first Mediciner was James Cumyne. The third was Gilbert Skene, author of a little book on plague of which only one copy exists (in the National Library of Scotland). It was entitled *Ane Breve Description of the Pest* and was the first original medical work to be printed in Scotland. It is dated, Edinburgh 1568.

After the time of Gilbert Skene, the office of Mediciner at Aberdeen lapsed for a time, and the next event of importance was the establishment of a second University, in 1593. King's College did not favor the changes wrought by the Reformation, and in consequence, George Keith, Earl Marischal, a zealous follower of Calvin, founded this rival University which still bears the name Marischal College. The two universities continued to work separately until their union in 1860. The students of both colleges were strictly disciplined under the watchful eyes of the "Regents" as the professors were called. Students were obliged to commence work at 6 a.m. and to be in bed by 9 p.m., although once a week

they were permitted to amuse themselves on the links. From the start, Medicine was taught at Marischal College, the first professor being Patrick Chalmers, whose ledger, still preserved, shows that malaria was prevalent in his time.

In the 16th century, Duncan Liddell (1561-1613), a distinguished son of Aberdeen who had been educated at King's College, held for some years the Chair of Medicine and Mathematics at the University of Helmstadt and amassed a considerable fortune, part of which, together with his library, he bequeathed to Marischal College on his death in 1613. There is a beautiful brass plaque to his memory in the Church of St. Nicholas.

The next step in advance, in 1741, was the establishment of an Infirmary for "poor persons who have distemper upon their bodies and such others as meet with the misfortunes of broken bones." It contained 20 beds and was the forerunner of the magnificent infirmary opened in 1936 which cost exactly one thousand times as much money to build. Medical education was furthered by the Aberdeen Medical Society, founded in 1789 by Sir James McGrigor who became Director General of the Army Medical Service and was celebrated for the excellence of his Reports on the Health of the Army. The Society was really a sort of extramural school and candidates for membership were obliged to pass an entrance examination in Osteology, Greek, and Latin.

No account of Aberdeen medicine is complete without some reference to the family of Gregory, which produced sixteen professors in various Universities. The first of them was James Gregory, Professor of Mathematics at St. Andrews. His son, James, was Mediciner at King's College and was, in turn, succeeded by James the younger (son), then by John (brother). John became Professor of Medicine at Edinburgh in 1766 and was the father of James Gregory who succeeded him in the Chair, and who was the originator of the famous Gregory's powder.

The teaching of Anatomy was of high standard in those early days. Andrew Moir was lecturer in 1831, when there was strong

feeling against anatomists owing to the nefarious doings of Burke and Hare in Edinburgh. Moir's dissecting room was burned down yet the lecturer maintained his prestige, continuing to teach until his death from typhoid fever at the age of 38. A later anatomist of great distinction was Sir John Struthers (1823-99), while Surgery was in the capable hands of Sir Alexander Ogston, who served abroad as a Surgeon in the war of 1914-18 and wrote an interesting book entitled "Memories of Three Campaigns." Aberdeen has had many other famous graduates, among them Sir Patrick Manson (1844-1922), "the father of Tropical Medicine."

GLASGOW, 1451

Now let us glance at the third great centre of medical learning, that of Glasgow. In the 16th century Glasgow was a town of subsidiary importance, with a population of only four or five thousand. The University had been founded by Bishop Turnbull in 1451 but Medicine was not actively taught for a long time. Andrew Boorde, physician, monk and traveller, who in 1547 wrote the first original English medical book to be printed—*A Breviario of Health*—visited Scotland during his wanderings and spent a year at what he called a "littyle unyversite named Glasco." This would appear to indicate that there may have been some medical teaching to attract him. Certainly there was a hospital, that of St. Nicholas, which had been founded by Bishop Muirhead in 1471, although very probably this was an almshouse, like Bishop Dunbar's hospital at Aberdeen. Later the Hospital of St. Nicholas came to be known as Provand's Lordship and it still stands—the oldest house in Glasgow—close to the Cathedral.

There was no organized control of the practice of medicine in and around Glasgow until the Faculty of Physicians and Surgeons was founded by Peter Lowe in 1599. At that date none of the Scottish Universities granted degrees in medicine but the Faculty was empowered to examine candidates and to decide whether they might be permitted to practice. Incidentally it may be remarked that Peter Lowe was a

Scottish surgeon who had served for over 20 years in the Army of France and had published in 1597 a *Discourse on the Whole Art of Chyrurgerie*, the first text book of surgery to be written in English. Peter Lowe's aim in founding the Faculty was to regulate and control medical practice in Glasgow. It was also resolved to give free medical treatment to the poor and even today this resolution is honored in spirit, if not in practice, since the Minutes of each meeting conclude with the words—"the poor were treated gratis, and the Faculty adjourned."

The teaching of Medicine in Glasgow University was very desultory and ineffective until the 18th century. The first professor of Medicine, Robert Mayne, was appointed in 1637 but he appears to have accomplished little. The real founder of the Medical School of Glasgow was William Cullen (1710-90). Born at Hamilton in 1710, he began his career as a general practitioner in his native town, in partnership with William Hunter. In or about 1744, Hunter went to London where he became a famous anatomist and obstetrician, and where he was joined by his more famous brother, John Hunter. Cullen meantime removed to Glasgow, and commenced his academic career as Professor of Medicine and Chemistry. With that versatility which was not uncommon at that day, he also taught Botany and Materia Medica. In 1755 Cullen was appointed Professor of Chemistry at Edinburgh, where later he succeeded to the Chair of Medicine on the death of John Gregory. Cullen was, in turn, succeeded by James Gregory of "powder" fame. Meanwhile the Glasgow Chair of Chemistry passed to Cullen's assistant, Joseph Black who, famous for his discovery of "latent heat," shares with Cullen the credit of establishing the Glasgow Medical School, which was well staffed and consolidated by the end of the 18th century.

The Royal Infirmary of Glasgow was opened in 1794, equipped with 150 beds and "two sedan chairs to convey patients to and from their homes." The end of the eighteenth century also witnessed the establishment of a second University, in 1796, by John Anderson, a man of great ability and

energy who had been Professor of Natural Philosophy since 1757. He intended to include faculties of law, theology, arts and medicine, but the medical faculty was the only one which really flourished and in the early years of the 19th century it became a formidable rival to Glasgow University. There were more than 700 students in 1830. Some years later the name was changed to the *Anderson College of Medicine*, and this institution continued to serve a useful function as an "extra-mural" school.

Meantime there were many distinguished teachers in Glasgow including Allen Thomson who taught anatomy and physiology successively at Edinburgh and Aberdeen and who eventually became Professor of Anatomy at Glasgow in 1848. His administrative ability was of great service to the University.

Of course, by far the greatest figure of the Glasgow Medical School was Joseph Lister, who went from Edinburgh in 1860 to become Professor of Surgery, and who introduced his antiseptic principle in 1865. His first paper on the subject appeared in the *Lancet* on March 16th, 1867 and was entitled "A New Method of Treating Compound Fracture." Thirteen cases were described, with one death and one amputation—a remarkable result at a time when such an injury was attended by high mortality and was almost invariably treated by amputation. When Lister returned to Edinburgh as Syme's successor, the Glasgow Chair was filled by Sir George Macleod and he, in turn, was followed by Sir William Macewen (1848-1924), whose works on the treatment of brain abscess and on the growth of bone are classic accomplishments.

The Chair of Medicine, in 1862, passed into the able hands of Sir William Tennant Gairdner (1824-1907) who in the following year became Glasgow's first Medical Officer of Health. When he assumed office, one third of all deaths in the city were the result of infectious disease, principally typhus fever, but under his able control the health of the city improved greatly. There were many other great physicians and surgeons, but enough has been said to prove the importance of the Glasgow School of Medicine.

EDINBURGH

Finally, let me try to give a brief outline of the rise and early development of the Edinburgh Medical School. I have kept it to the end, as Edinburgh is the youngest of the Scottish Universities, founded in 1583. Nevertheless Anatomy and Surgery have been subjects of instruction at Edinburgh since the beginning of the 16th century. It was during the reign of King James IV of Scotland, who has already been mentioned as a patron of medicine, that the Barber Surgeons of Edinburgh obtained their Charter from the Town Council in the year 1505. The "Seal of Cause," as it was called, empowered the Barber Surgeons to decide, by examination, who was to practice within the Burgh. Candidates were to be able to "baith read and write" and were to be familiar with "the anatomy of man's body" and the position of the veins, venesection being then the treatment for many ills. Furthermore, the Incorporation of Barber Surgeons, which later became the Royal College of Surgeons of Edinburgh, was entitled to claim the body of one executed criminal each year for dissection purposes and, strangest of all regulations, was to have a monopoly of the sale of alcoholic liquor (*aqua vitae*). Unfortunately this monopoly has not been retained. The early meeting place of the Barber Surgeons was a mean street called Dickson's Close. There was some intermittent teaching of anatomy during those early days, but a great impetus to learning was given in 1583, when the Town Council established the Town's, or "Tounis," College. So determined were they that their institution was to be free from what they termed "medieval papistry" that they did not apply to it the name "University." At first, there was no provision for the teaching of medicine, but an important step in advance was the foundation of the Royal College of Physicians in 1681 by Sir Robert Sibbald, who had studied at Leyden and who was the author of important works on history and geography, as well as Medicine. Sibbald and his young colleague, Dr. Archibald Pitcairne, were appointed Professors of Medicine in the Town's College in 1685

They were also instrumental in establishing the Physic Garden, then an important adjunct to the teaching of medicine, on the site of the present Waverley Station. It was the precursor of the present fine Royal Botanic Garden.

Pitcairne attained a European distinction when he was appointed Professor of Medicine at Leyden in 1692, an appointment which was then possible, as language difficulties did not exist because all teaching was conducted in Latin. Among his pupils at Leyden was Hermann Boerhaave, who succeeded him, and who became perhaps the greatest teacher of Medicine of all time.

In those days the links between Edinburgh and Leyden were numerous and strong. Firmest of all was that forged by John Monro, a surgeon in the Army of William of Orange, who was so greatly impressed by the Leyden methods that he resolved that Edinburgh should have a Medical School, conducted on similar principles. Accordingly, he educated his son Alexander at Leyden with a view to having him appointed Professor of Anatomy at Edinburgh. This ambitious plan proved most successful. Alexander Monro assumed the Chair in 1720, and thus became the "Father" of the Edinburgh Medical School. He was succeeded by his son, Alexander Monro, secundus, who was followed in turn by the grandson, Alexander Monro, tertius. Monro secundus maintained the tradition of his father, indeed he was even more distinguished, but Monro tertius was content to read his grandfather's notes, over a century old, to his class, without even deleting the remark, "When I was a student at Leyden in 1719."

The Monros held the Chair for 128 years. But there were other noteworthy anatomists. Sir Charles Bell (1774-1842) commenced and ended his career in Edinburgh, but most of his great work on the nervous system was carried out in London. One of the great Edinburgh teachers of anatomy was John Barclay (1758-1826), who was obliged to deliver the same lecture twice a day in order to accommodate his large class. He was succeeded by Robert Knox (1791-1862), an admirable lecturer whose classes were very popular, and a man of high sci-

entific attainment. Unfortunately, his career was clouded by his unwitting association with the Burke and Hare murders in 1828. One of Barclay's assistants who became a famous surgeon was Robert Liston (1794-1847). Robert Liston and James Syme (1799-1870) were closely associated as teachers of anatomy in Edinburgh until, in 1835, Liston became Professor of Surgery to University College, London, where he was the first surgeon to employ ether as a general anaesthetic.

The anaesthetic value of chloroform was discovered by the Professor of Obstetrics, Sir J. Y. Simpson, in 1847. Simpson was a versatile man, although his incursion into the field of surgery made him unpopular with some of his surgical colleagues. He was one of those who opposed Lister's ideas, alleging that the prevalence of septic infection was due to faulty hospital construction, or "hospitalism," as it was called.

The first medical man in Edinburgh to confine his practice to surgery was Benjamin Bell, who lived at the end of the 18th century, who wrote a well known textbook of Surgery, and who was the direct ancestor of Dr. Joseph Bell, the Edinburgh surgeon, the original of Sherlock Holmes.

Benjamin Bell was one of the earliest surgeons to the Edinburgh Royal Infirmary, which was opened in 1741 and provided for 200 sick persons "each in a distinct bed." Before that day it was not uncommon for two patients to occupy the same bed. The greatest Edinburgh surgeon before the time of Lister was Lister's father-in-law, James Syme, of whom it was

said that he never wasted "a word, a drop of ink, or a drop of blood." When Syme failed to secure appointment to the Infirmary Staff he established a hospital of his own, and that hospital, Minto House, was the scene of the operation described in *Rab and his Friends* by Dr. John Brown, who was Syme's house surgeon.*

The wonderful work of Lister, continued at Edinburgh when he succeeded Syme in the Chair of Clinical Surgery, deserves a lecture to itself. Nor is it possible within the bounds of this outline, to discuss the progress of other subjects in the medical curriculum, the contribution to medicine of William Cullen, of James Gregory and, in later times, of Sir Robert Christison (1797-1882) and many others who taught various medical subjects in the University and in the extramural School of the Royal Colleges. As time went on, and as other Medical Schools became established, Edinburgh ceased to be the main centre of medical education in Britain, although it still maintains a high standard and attracts many students, both undergraduates and post-graduates. Among them there have been many American students ever since the early years of the eighteenth century when the torch of medical learning, re-kindled and strengthened by Leyden and Edinburgh, was handed on, across the Atlantic, to Philadelphia and to New York. The close friendship then established remains firmer than ever.

* After this lecture Dr. Douglas Guthrie presented to the Library of The New York Academy a copy of the first illustrated edition of *Rab and his Friends*.

SECTION ON MICROBIOLOGY

FEBRUARY 16, 1949

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I. EXECUTIVE SESSION

Reading of the Minutes

II. PAPERS OF THE EVENING

a. Introduction to studies on the common cold

Alphonse R. Dochez

College of Physicians and Surgeons
Columbia UniversityGREGORY SHWARTZMAN
Chairman

The Mount Sinai Hospital

b. Research on the common cold

Norman H. Topping (by invitation)

Leon T. Atlas (by invitation)
National Institute of Health
Bethesda

c. Secondary invaders in reference to the epidemiology of the common cold

Yale Kneeland (by invitation)
College of Physicians and Surgeons
Columbia UniversityHARRY MOST
SecretaryNew York University
College of Medicine

Introduction to Studies on the Common Cold

A. R. DOCHEZ

If we examine ancient accounts of disease we easily discover the description of a group of respiratory symptoms that exactly represents the clinical manifestations of what today we call the common cold. That it is an ancient disease and that it has continuously maintained its characteristic picture there can be very little doubt. The cold seems to be firmly established as a human disease whose character and high incidence have remained unaltered throughout the centuries. Its causative agent must therefore be, in the terms of Theobald Smith, a most efficient parasite.

For many years curiosity concerning the causation of the cold has remained active and has, especially during the period of modern bacteriology, stimulated the research activity of numerous investigators. With

the development and improvement of bacteriologic techniques study of the throat and nasal flora of individuals suffering from the common cold has been the subject of repeated investigations. A number of well-characterized microorganisms have been described as being associated with certain outbreaks of the disease or with individual attacks. In general these organisms comprise Gram-positive cocci, Gram-negative cocci, such as *Micrococcus catarrhalis*, diphtheroid bacilli and a number of others. A specific causative relationship of these organisms to the disease has been difficult to establish convincingly because of their presence, without the production of symptoms, more or less continuously or for varying periods of time in the respiratory flora of healthy individuals.

In order to evaluate the pathogenic importance of the organisms mentioned above my colleagues and myself have studied a number of human subjects during healthy periods in order to gain complete familiarity with their nasopharyngeal flora. Later when any one of these individuals contracted a cold very careful bacteriological observations were made in order to ascertain if there appeared for the first time or in significantly increased numbers any easily recognizable organism to which a causative role might be assigned.

The results of these studies led us to certain conclusions. In the early days of the cold no new organisms appeared in the throat flora nor was there any significant increase in such potential pathogens as were already present. In fact, there generally appeared a diminution in the total number of organisms present, due in all probability to dilution by the increased amount of secretion. Whenever there was evidence of increased activity this usually occurred late and was frequently associated with some complication which had developed. Our observations led us to conclude that the common pathogens of the nasopharynx, in general, are not the initiating agents of infection of the respiratory tract of the type of common cold and that they act principally as secondary invaders of an inflammatory process causatively induced by a primary agent of unknown character.

With increasing knowledge of the pathogenic importance in infectious diseases of filterable viruses research turned toward the investigation of the possible relationship of such microorganisms to the common cold. Early important studies were those of Kruse¹ in 1914, Foster² in 1916, and Olitsky and McCartney³ in 1923.

Kruse realizing the inadequacy of the evidence for a bacterial etiology studied the possibility of virus causation. He performed two experiments on students in which he inoculated the subjects intranasally with bacteria-free filtrates of nasopharyngeal washings from individuals with typical acute colds. In the first experiment positive results were obtained in four out of five volunteers. The incubation period was from 1-3 days. In the second experiment fifteen of thirty-

six were positive in from 1-4 days. The incidence of spontaneous colds at the time was very low.

Foster in 1916 performed a similar set of experiments. Seven out of ten soldier volunteers were positive with one possible contact infection. Foster then attempted to cultivate the virus in Smith-Noguchi medium. Two strains were cultivated. The cultures showed a haze spreading from the area of the tissue. Small globoid bodies could be stained which appeared motile. Eleven volunteers were inoculated with the culture material and all manifested typical symptoms and characteristic appearance in the throat. Cultures from the subjects were positive for the growth of globoid bodies. Colonies were demonstrated in agar ascitic fluid. From what we know today the globoid bodies observed may have been due to small filterable Gram-negative bacteria which are constantly present in the normal throat. Some of these organisms are motile. It is possible that a true filterable virus was also present, which would account for the reproduction of the common cold in individuals inoculated with culture material.

Later studies⁴ confirmed the transfer of colds from human to human by means of bacteria-free filtrates of throat washings obtained from individuals with colds. In at least one instance this infection was transferred from individual to individual in series.

In 1926 my colleagues and myself investigated the possible virus etiology of the common cold. Having learned from Dr. Francis G. Blake that chimpanzees were subject to colds resembling in every particular the human cold these animals were chosen as experimental animals. After establishing a careful quarantine, inoculation of bacteria-free material obtained from examples of typical human colds was performed. In a large percentage of instances the chimpanzees came down with colds similar in every respect to their own spontaneous colds and to the same infection in human beings. The cold could be passed from chimpanzee to chimpanzee using the established technique, and infection of healthy cage contacts also occurred. The incubation period of the disease was from 24-48 hours.

In view of the mild character of the experimental disease in animals, a similar study was made using human volunteers as subjects. The results obtained were essentially the same as those obtained with chimpanzees. The infection could also be transferred from human to human in series. The virus etiology of the common cold was thus established.

The next procedure was an attempt to cultivate the virus *in vitro*. Chick embryo medium was first used and the experiment proved successful. Large numbers of human beings were successfully infected with the tissue culture material and in one instance the culture remained infective for at least eighty transfers. Later the embryonated hen's egg was used for purposes of cultivation and successful experimental inoculations resulted. The number of egg transfers was relatively small, in one instance three and in another a few more.

No determinable changes could be observed in the medium in which the virus grew. All attempts to establish the culture virus in laboratory animals were failures. No significant tests for the presence of the virus in the culture medium could be developed either *in vitro* or *in vivo*. The virus was studied in many ways but no progress beyond animal and human inoculation took place.

The practical objective of this work was the development of a useful form of prophylactic inoculation. A number of in-

dividuals were injected with a living virus vaccine but successful immunization did not result. A number of facts militate against the success of such an undertaking, the lack of an enduring immunity following a spontaneous attack of the common cold and the absence of knowledge concerning the number of immunologic varieties of the virus of the common cold. Before further progress can be made there must be further development of the techniques for the study of the common cold virus and a great deal must be learned concerning the natural infection in man, particularly in respect to increased resistance to infection, if indeed such exists.

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Research on the Common Cold

NORMAN H. TOPPING

It has been 34 years since Kruse¹ reported that he had produced the common cold in human volunteers by inoculation of filtered nasal secretions from an assistant with a cold.

In the last 25 years great progress has been made in studies on viruses but up until the last 2 or 3 years there has been relatively little advance in our knowledge

of the agent or agents of the common cold.

Kruse produced colds in 33 per cent of his first group of volunteers, the majority within 1 to 3 days after inoculation with a Berkfield filtrate of nasal washings. He was able to produce symptoms of common cold in 42 per cent of another group studied later, again the majority showing an incubation period of 1 to 3 days.

Foster² confirmed and extended Kruse's observations as to the human-to-human transmission of colds and its filtrable nature in 1916-17. In 1930 Long, Doull, Bourn and McComb³ produced upper respiratory infections in 11 out of 19 human volunteers, using nasal washings from an individual with a cold, and the same year Dochez, Shibley and Mills⁴ gave further confirmation, and also demonstrated the transmissibility of human disease to anthropoid apes. Forty-four per cent of human volunteers and apes developed the disease syndrome; the humans exhibiting symptoms usually within 24 hours and the apes within 36-48 hours after inoculation. The infective agent was cultured under anaerobic conditions in the hashed tissues of 8-10 day old chick embryos.

The hashed-chick-embryo culture method of Dochez was confirmed by Powell and Clowes⁵ in 1931. A variation of this method of cultivating the cold virus was reported in 1936 by Kneeland, Mills and Dochez.⁶ Instead of using hashed-chick-embryo tissue, they described successful cultivation of the virus in the chorio-allantoic membrane of the developing chick embryo. The literature does not reveal later confirmation of this method for culturing the cold virus.

The pattern revealed in these reports of work done from the beginning of World War I to the period of World War II is one of confirming the existence of a filtrable infectious agent, or a group of such agents, capable of transmitting the common cold from an infected to a non-infected human under experimental conditions. Considerable ancillary research went forward, such as improvements in methods for obtaining the infective material, improvements in cultural media, and refinements in methods for preparation of the inoculum and its administration to volunteers. In addition, there were studies on the normal bacterial flora of the nose and throat, and on the variations in the flora occurring during colds. Various epidemiological studies were of interest to public health authorities but contributed little to the etiology of the disease.

During World War II the Office of the Surgeon General, U. S. Army, established

a Commission on Acute Respiratory Diseases. Certain of the findings of this Commission may have considerable significance. One of the most important was the report⁷ that two distinct common cold disease entities had apparently been discovered. The Commission demonstrated by experimental methods that two distinct types of minor respiratory illness could be transmitted to human volunteers. Among the several differences between the two diseases was the incubation period, i.e.—1 to 2 days and 5 to 6 days. Of even greater interest was the report that positive immunity was developed in humans against reinoculation with the virus of the disease characterized by a long incubation period, whereas no immunity was produced in volunteers reinoculated with virus obtained from an individual having the illness of short incubation period. Neither disease conferred immunity upon challenge by the apparent causative agent of atypical pneumonia.

The investigators felt that "these findings provide additional proof that at least two filtrable agents, or viruses, may induce minor respiratory illness in man, and suggest that these agents are probably distinct from the virus or viruses of primary atypical pneumonia."

An interesting report was made in 1947 by Pollard and Caplovitz⁸ to the effect that they had succeeded in cultivating "the agent of the common cold" in the chorio-allantoic fluid of embryonated eggs. Subcutaneous inoculation with their cultured material in 2 doses of 1 cc. at weekly intervals was reported to have protected volunteers challenged intranasally with Seitz filtrates of nasal washings from naturally acquired cases of common cold.

In a personal communication Andrews⁹ stated that using two similar strains of filtered nasal washings he was able to reproduce symptoms of minor respiratory disease in about 50 per cent of human volunteers. Filtration studies of these agents suggested a particle size similar to or smaller than that of the influenza viruses.

In December 1947, Topping and Atlas of the Common Cold Unit, National Institute of Health,¹⁰ published a preliminary note describing the results of an attempt

to isolate, cultivate and identify the agent or agents of the common cold. Unfiltered nasal washings obtained from individuals within 24 hours of the onset of cold symptoms produced signs and symptoms of minor upper respiratory infection in five out of five volunteers in 36 to 48 hours. All five complained of fatigue, nasal obstruction, and frequent expectoration. Three complained also of sneezing, headaches, coughing, and burning, watery eyes. Two experienced prodromal chilly sensations and hot flashes. Objectively, hyperemic obstructed nasal passages, red throats with prominent lymphoid follicles, and large quantities of postnasal mucus for 2-5 days were evident. Slight temperature elevations between 99° and 99.6° developed after onset. One volunteer suffered all the above complaints to a more severe extent, and in addition developed moderate rhinitis, a mild laryngitis for a day, moderate pharyngitis, episodes of sharp, sticking pains subternally for 3 days (X-rays normal) and a temperature elevation to 102°F. for a day.

Nasal washings from the volunteer who developed the more severe clinical disease were inoculated into embryonated hen eggs and several substrains were obtained after varying numbers of allantoic passages. One of these substrains produced a mild illness similar to that in the original volunteer group. Another substrain produced 100 per cent illness of a more severe type in 14 volunteers.

Within 7-24 hours all patients in this group complained of dry, irritated throats (without objective pharyngitis) and exhibited malaise out of proportion to physical findings. Within a few hours nasal obstruction and postnasal discharge with frequent expectoration developed and remained prominent during the course. All complained of frequent supraorbital headaches, moderate sneezing, and an infrequent, mild, unproductive cough. Hoarseness was evident in 9, one of whom became aphonic for about 12 hours. Nine complained of burning, watering eyes (with mild conjunctivitis objectively) and vague chest aches without significant X-ray findings. Intervals of profuse serous rhinitis were observed in five. Early in the illness, five complained of

chilly sensations and hot flashes. Objective signs of pharyngitis, lymphoid follicular prominence, hyperemic obstructed nasal passages, and profuse postnasal discharge were observed in all. Temperatures between 99° and 100°F. occurred at irregular intervals in 12 volunteers. No significant urine or white blood count changes were apparent.

Sixth- and seventh-passage allantoic fluids containing this substrain produced moderately severe illness in fifteen out of sixteen, and fourteen out of sixteen volunteers respectively.

In sum, sixty individuals in eight groups were inoculated with allantoic fluid containing this agent. Of the sixty, fifty-seven developed a characteristic syndrome reminiscent of the minor upper respiratory infection of the donor. Microscopic studies have failed to reveal bodies suggestive of bacteria or the larger viruses. On the other hand, preliminary electron microscopic examinations have shown characteristic particles of the same general size as viruses of the influenza type, but readily distinguishable from them.

A number of further studies are being made by the Common Cold Unit of the National Institute of Health. Among these are:

Attempts to determine by laboratory and human volunteer tests whether different disease entities are involved in the minor respiratory illness known as "the common cold."

Determinations regarding immunity that may be conferred by agents of minor respiratory illness.

Duration of infectious spread in humans of illness produced by these agents.

Physiological studies, including blood and urine chemistry balance during infection.

Quantitative nasal flora changes during periods of infection.

Differences in epidemiology of the disease according to mode of inoculation.

Reisolation of virus from volunteers infected with egg material.

Concentration of virus by various procedures which keep it alive so that particles of only one type can be visualized under the electron microscope.

In addition to the research of the Com-

mon Cold Unit of the National Institute of Health, the U. S. Public Health Service is supporting common cold research by other groups through its research grant program.

It is clear from evidence of past work that the common cold has been one of the most complex and difficult medical research problems. It is equally clear that here is a problem wherein substantial progress demands coördinated, concerted teamwork by patient and careful investigators representing many scientific disciplines. The biochemist and the biophysicist, the clinician and the epidemiologist are only some of those who must contribute their special skills.

The incentive for coördinated hard and patient work to solve the problem of the common cold is more than merely advancement of scientific and medical knowledge. The real challenge is found in the fact that the common cold is the most prevalent and the most highly infectious of all the communicable diseases. There is general agreement among investigators in this field that the average person suffers at least two colds in the course of a year, giving a total of approximately 300,000,000 colds annually for the general population of this nation. The duration of a simple cold averages about five days. Thus, multiplying the number of colds by their duration, one finds that the people of the United States each year suffer about 1,500,000,000 days of discomfort and reduced efficiency, if not of actual disability, from this cause.

Various studies indicate that from 40 to 50 per cent of all days lost from work are attributable to colds and their complications. It has been conservatively estimated that the toll of the common cold in this country is at least one working day per employee per annum. If that is so, there will be more than 60,000,000 days lost to industry this year because of colds. Even at an average daily wage of \$7, the loss in wages totals more than \$420,000,000.

The cost of drugs and medical care must also be added. Accurate statistics on this subject are not available, so that it is

necessary to resort to speculative estimates. On the assumption that every family in the United States spends on an average of \$10 a year for drugs and medical care in the treatment of colds, the total amount spent for these items would be in the neighborhood of \$100,000,000.

The cost to employers resulting from lost production and disrupted routine is extremely difficult to estimate. It is certain, however, that the annual cost of colds to employers is very considerable for the country as a whole.

On the basis of the figures cited above, it is thus estimated that the cost of the common cold to the American people is well over a billion dollars a year. Although the common cold is generally considered a minor infection, any disease that runs to such astronomical figures in cost must be rated high in the list of enemies of the public health.*

* Source: Statistical Bulletin. Metropolitan Life Insurance Company, Vol. 28, No. 11, November 1947, pp. 6-7.

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The Relationship of Bacteria to the Common Cold

YALE KNEELAND, JR.

This subject is a complex and surprisingly vague one. Much of the available data are very old, and in the forthcoming discussion I shall lean heavily on work done many years ago by ourselves and others. To begin with, I am going to pose four questions, and the discussion will take the form of an attempt to answer them. The four questions are as follows:

1. What bacteria are important in common upper respiratory infection?
2. Can and do bacteria initiate colds?
3. If not, what role do they play in colds?
4. What relationship do they have to epidemiology?

Let us now attempt to frame answers to these in order:

1. β hemolytic streptococci, *H. influenzae* and pneumococci need no defense as respiratory pathogens, and I am going to assume that they are pathogenic. I assume that Friedländer's bacillus is also a pathogen, but it is sufficiently rare so that I am going to omit it from the discussion. Abundant studies of respiratory bacteriology for many years have indicated that various *Neisseria*, non-hemolytic streptococci, diphtheroids, etc. constitute the normal "basal flora," and are not significant in disease. I am going to add staphylococci to this basal flora, for although they may occasionally act as secondary invaders, I believe that this role has been considerably over-emphasized in the past, particularly by otologists. The discussion, therefore, will revolve around hemolytic streptococcus, *H. influenzae*, and the pneumococcus.

2. Can and do bacteria initiate colds? If we consider our three pathogenic organisms one by one, the idea of exudative pharyngitis due to hemolytic streptococcus immediately comes to mind. "Strep. throat," "follicular tonsillitis"—certainly this is a clinical entity of which the hemolytic streptococcus is commonly believed to be the

cause. But can a virus component in the etiology be dismissed? It seems to me that it can be. For one thing, some of the most florid outbreaks of this condition have been shown to be milk- or food-borne. Moreover, the spread of hemolytic streptococci in hospitals, particularly from nasal carriers, was carefully studied in the last war, and there was no evidence of a virus component. It would appear, therefore, that the hemolytic streptococcus may be a primary incitant of common respiratory disease—but it causes "strep. throat," and this is *not* the common cold.

In regard to *H. influenzae* and the pneumococcus, no strictly analogous situation exists. To be sure, there have been rare outbreaks of disease such as the so-called "Woodside throat" in Australia at the beginning of the last war, which were believed due to a primary *H. influenzae* pharyngitis of very severe character. Cooke et al.¹ adduced some evidence against a virus component here, but it was not conclusive. On the other hand, our own studies² as well as those of others, would indicate that when nose and throat cultures are taken in the same individuals regularly, both *H. influenzae* and pneumococci may appear and disappear in a manner apparently unrelated to attacks of the common cold. Even in the well-known studies of semi-isolated communities by Burky and Smillie,³ where these organisms were prominent during epidemics respectively in Labrador and Alabama, they could not be recovered in every case, and appeared late in many of the cases. The classical study of the completely isolated community (Spitzbergen) was reported by Paul and Freese in 1933.⁴ It will be remembered that from December 1 until the end of May, the period when this little community was ice-bound, only 19 colds occurred among 500 inhabitants. Moreover, during the last

3 months of the period there were only four, three being in the same individual. Yet *H. influenzae* and pneumococci (as well as hemolytic streptococci) were recovered from the population throughout these winter months—and with about the same frequency as they were found when colds suddenly became rampant following the arrival of the first boat in the Spring. This whole experience powerfully suggested that bacteria were not the inciting agents of the common cold, at least of the communicable type, and the presence of a virus was naturally inferred. In reviewing all the evidence over the years, one is led to the conclusion that, while there is no proof that bacteria cannot cause colds, ordinarily they do not.

3. What role do pathogenic bacteria play in the common cold? It is very tempting to say that they act as "secondary invaders," and let the matter rest there. Yet when one studies the available evidence, it is extraordinary how difficult it is to define their function as secondary invaders. Dingle and his co-workers,² for instance, after exhaustive studies of acute respiratory disease in the Army, came to certain beliefs in regard to the streptococcus. For one thing, they concluded that hemolytic streptococcus caused only about a quarter of the cases clinically designated as "exudative pharyngitis," and where it was not etiologically significant the mere presence of streptococci did not affect the course of the disease. On the other hand, Coburn⁶ reported that mass sulfadiazine prophylaxis in the Navy resulted in a marked reduction in hospital admission rate. He stated that the morbidity rate for virus diseases remained unaffected, but the data suggest that the principal result of prophylaxis was the virtual elimination of frank streptococcus disease in a highly susceptible population.

The pneumococcus presents a somewhat different problem. Experiences in our own infants and chimpanzees^{7,8} both of which are highly susceptible to severe colds, indicated that the presence of this organism appeared related to the severity of the common cold. The same finding was made by Burky and Smillie³ amongst Alabama

school children. Another method of approaching the problem is by the use of specific chemotherapy or antibiotics. Siegel,⁹ working at Letchworth Village with retarded children as subjects, concluded that early sulfadiazine treatment of common respiratory disease reduced the duration of fever, general severity, and complications in a controlled series. Lapin¹⁰ gave oral penicillin to 160 children for a year and found the days of fever reduced from 24 to 5, and the number of febrile respiratory infections from 5.6 to 1.8 per child as compared with the previous year. Minor coryza, however, continued. On the other hand, Rusk and Van Ravenswaay¹¹ working with military personnel, a less highly susceptible population, found that sulfadiazine treatment of common respiratory disease did not affect the duration of fever or the length of hospital stay.

The situation in regard to *H. influenzae* would appear to be analogous to that of the pneumococcus. Burky and Smillie³ made very similar observations of its behavior in Labrador to that of the pneumococcus in Alabama. We have noted it in severe colds both in the infant and in the chimpanzee. If we attempt to sum up, then it would appear that the role of the streptococcus is equivocal in instances where it is not the primary incitant of disease, and that pneumococcus and *H. influenzae* can enhance the clinical severity of colds in highly susceptible individuals, and produce such complications as sinusitis, otitis, and pneumonia. On the other hand, most of the effects of the common cold in adults are probably due to the virus and not to bacteria.

4. Are bacteria related to epidemiology? Again, the evidence on this point is rather scanty, and tends to be indirect. We observed¹² in the chimpanzee a shift from the R to the S form of *H. influenzae* in throat cultures taken during spontaneous and experimental colds. In free intervals only the R form could be recovered, but with infection a reversion took place to the same S type as that obtained during the previous cold. This highly suggestive example of interaction of virus and bacterium has never

been duplicated in man. In another very susceptible type, however,—the human infant—we have noted some apparent relationship of the two types of agents. In a group studied throughout one winter¹² it was believed that the first Autumn wave of colds, presumably of virus origin, resulted in a widespread dissemination of pneumococci. Then, later on, when the carrier rate was 80 per cent or thereabouts, an outbreak of colds took place which showed not only considerably increased clinical severity, but also a higher incidence. It is also worthy of note that in Burky and Smillie's experience³ the outbreak of colds in Alabama and Labrador—again in very susceptible populations — associated with pneumococcus and *H. influenzae*, also showed this clinical severity and high incidence.

With such evidence as this before us, it is permissible to frame a tentative answer to the last question. One action of the virus may be to increase the dissemination of pathogenic bacteria, and perhaps in certain instances to alter their essential virulence. With the ground thus prepared, the same or another viral agent, acting in conjunction with bacterial agents, may be more highly communicable and more infective.

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BULLETIN OF THE NEW YORK
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CONTENTS

- Present Status of Electric Shock Therapy 541
Lothar B. Kalinowsky

- The Medical, Social and Public Health Aspects of
Rehabilitation 554
Howard A. Rusk

- Concerning Voluntary and Involuntary Movements . . . 566
Abraham M. Rabiner

- Psychiatric Perspectives of Today 577
Gregory Zilboorg

- Hospitalization of Veterans 587
*A Report by the Committee on Public Health
Relations of The New York Academy of Medicine*

Library Notes:

- Recent Accessions to the Library 601
-

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BULLETIN OF
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SEPTEMBER 1949

PRESENT STATUS OF
ELECTRIC SHOCK THERAPY *

LOTHAR B. KALINOWSKY

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AFTER ten years of personal experience with electric convulsive therapy (ECT)¹ a survey of the present status of this treatment is a welcome opportunity to take stock of established facts, questions still under dispute and the limits of our present knowledge. In psychiatry such critical reviews are more important than in other fields of medicine, because the split among psychiatric schools on questions of theory makes the acceptance of clinical facts more difficult. This is all the more true for the somatic treatments in psychiatry, because they strongly contradict the theoretical concepts of many psychiatrists.

Theoretical objections against electric shock treatment are so frequently and so violently voiced that it seems justified to make some general remarks before a detailed discussion of various aspects of the treatment is given. It is true that no adequate theory for ECT is available, but this is no valid reason against its application. The patient who needs help, cannot wait until empirical knowledge has found a satisfactory theoretical basis. In most psychiatric conditions we do not know the etiology, and, therefore, cannot expect to understand the

* From the New York State Psychiatric Institute and Hospital, New York. Given before the Stated Meeting of The New York Academy of Medicine, March 3, 1949.

mechanism of a treatment which was found on empirical grounds.

Equally immaterial is the objection that ECT is only a symptomatic treatment. When we remove an involuntional melancholia or an acute schizophrenic psychosis, we achieve more than a symptomatic improvement. But even in those cases where ECT only leads to a temporary improvement, its use can be valuable, and no one will object to insulin in diabetes on the grounds that its effect lasts only for hours.

Psychiatry is in great danger of becoming dogmatic when it postulates that only one type of treatment should be used to the exclusion of all the others. Those of us who for many years knew psychotherapy as the only available tool in psychiatry, are glad that, as in other fields of medicine, different procedures become available, and that we learn to discriminate in applying our various therapeutic techniques.

The original technique with alternating 60 cycle current, as introduced by Cerletti and Bini,² is still the standard procedure. Their bitemporal application of a forceps system of electrodes is unjustly abandoned by many manufacturers of machines. The forceps electrodes are far more practical in the treatment of uncoöperative patients than electrodes fastened with rubber bands. Of the many machines recommended by competing manufacturers the least complicated ones should be preferred, because they are less apt to present mechanical troubles. A successful solution requires only the continued efforts to find a type of current which abolishes some of the unpleasant side-effects of ECT. These attempts can be summarized as follows: The first claim of reducing post-treatment memory impairment was made by Friedman and Wilcox³ who introduced a unidirectional current in which only one phase of the usual biphasic current is used. Lessening of memory impairment and of electroencephalographic changes were claimed but this effect was more definite in the subsequent development by Liberson⁴ of a brief stimuli technique. Recently, Wilcox, too, replaced his unidirectional long stimuli with brief stimuli of about 500 per second, while Liberson reduced the number of stimuli to 120 per second with a duration of .5 to 1.0 milliseconds for the individual stimulus. These newer techniques produce convulsions with a lower amount of current applied for a longer period of time. It should be pointed out that this can be done equally well with the usual 60 cycle current, but was avoided because lower milliamperage is usually felt by the patient. It is admitted that for this same reason many patients treated with the

more recent modifications of ECT become apprehensive of the treatment. Since we, thus, lose the greatest advantage of ECT, the newer techniques are not generally accepted and have been given up by a number of experienced workers who have tried them. Whether the advantage of lesser memory impairment which was actually never confirmed in comparative studies, is really due to the different type of current or to such other variables like vertex-temporal application of the electrodes, is the subject of an investigation now under way at the Psychiatric Institute. Among many other techniques, Delmas-Marsalet's method with pulsating direct current,⁵ Strauss and MacPhail's steep wave electroplexy,⁶ and Larragoiti's brief stimuli technique⁷ with three electrode—vertex and bitemporal—application may be mentioned. They all have the same therapeutic results, because not the electric current but the convulsions are therapeutically effective. Memory impairment is certainly not explained by a higher current intensity. We are now using two or three stimuli routinely in each treatment for reasons given later, and yet, the patients show no more confusion than before we used this technique. Reports on these techniques often mentioned "slight" seizures whose descriptions resemble incomplete seizures. In our experience such incomplete seizures followed by quick awakening are therapeutically ineffective. This is also true for the rarely encountered Jacksonian seizures and for subconvulsive (petit mal) responses.

While those recommending the technical modifications mentioned so far, did not claim better therapeutic results, this was done by some workers for the so-called Electronarcosis Treatment⁸ which applies electric stimulation for 7 or more minutes. After a personal experience of two years with this method, I am unable to see any advantage over ECT; to the contrary, since it is cumbersome, frequently felt by the patient, and certainly more dangerous, as shown by Garmany and Early,⁹ I decided to give it up. The term "Electronarcosis" is unjustified, because the patient has a generalized seizure. After a typical tonic phase, the clonic movements are suppressed by the continued flow of current; when after 30 seconds the current is reduced, the last clonic movements of the convulsion still become visible. When the current is stepped up again, the patient remains in a rigid state which does not seem to have any therapeutic value and during which some patients become restless and begin to feel the current. Bowman

and Simon¹⁰ have shown that patients with depressions need the same number of applications as were necessary in previous episodes treated with ordinary ECT, and that there is no evidence of a superiority in any type of schizophrenia. It is true that some favorable reports have appeared,^{11,12} but no convincing statistical proof of its claimed superiority over ECT or even over insulin was given.

ECT has the great advantage of being a surprisingly harmless procedure and any recommendations complicating its simplicity should be carefully tested as to their safety. Convulsions seem to be a preformed mechanism which can be safely elicited in every individual. This explains why fatalities in uncomplicated ECT are practically unknown, and why preëxisting diseases are hardly aggravated by the treatment. Hypertension and myocardial damage, so frequent in the group of involutional agitated depressions, are not likely to increase during a convulsive treatment. This should be known to all psychiatrists, and it is unfair to shift the responsibility for the treatment of such patients to a medical consultant who is unacquainted with the fact that in such cases the cardiovascular condition improves as soon as the strain of the emotional disturbance is removed. Tuberculosis is also no contraindication for ECT. In view of the frequent simultaneous occurrence of tuberculosis and schizophrenia, it is regrettable that some hospitals still preclude such patients from treatment of their psychotic condition. The constant gain of weight after successful ECT was often seen to improve the condition of tuberculous patients. Pregnant women were treated in the last month of their pregnancy without any harm to mother or child. The fact that in epileptics other diseases are not aggravated by the convulsions, explains why most of the originally postulated contraindications for ECT were unjustified. It may be mentioned that children¹³ as well as patients beyond seventy and eighty years of age¹⁴ can be safely treated.

The most harassing complication of ECT continues to be the occurrence of fractures. Those of the mid-thoracic spine are of limited clinical importance and never lead to any serious consequences; continuation of treatment where necessary, does not increase the degree of compression. We do not know of any instance where X-ray findings prior to treatment could have predicted such occurrence, and it is unjustified to consider arthritis or old deformities of the spine as contraindications. A more serious problem are the fractures of the

long bones, particularly humerus and femur, and those rare but often bilateral fractures of the acetabulum. It should be stated emphatically that there is no way of predicting such fractures. In our large treatment group we never had fractures of the long bones, but in a much smaller material in another hospital, the author had several such instances with the same technique. Special position of the patient hardly prevents fractures, but they are favored by tight restraint. As a preventive measure we routinely induce a subconvulsive response in order to make the patient relaxed before the convulsive stimulus is applied. Another attempt to prevent fractures is the slow stepping-up of the current, the so-called glissando technique (Tietz), which we found unreliable.

A reliable but dangerous method to prevent fractures is the use of curare (Intocostin Squibb).¹⁵ Our own experience and increasing evidence in the literature show that curare is more dangerous than the complications it is supposed to prevent. Contrary to uncombined ECT, several fatalities in patients treated with curare were reported, and others in patients who died from the injection of curare even before the convulsion was induced,¹⁶ are sufficient warning against routine application of this drug; we consider it valuable, however, in patients where preëxisting bone pathology such as Paget's disease or recent fractures would otherwise preclude a strongly indicated course of ECT.

Less dangerous but also complicating the treatment is the preliminary use of intravenous sodium amytal or pentothal in ECT. These drugs increase the patient's respiratory difficulties which are anyway the most frequent complication in ECT which we counteract by routine application of a few artificial respiratory movements. Lessening of muscular contraction and of the strain on the heart as a motivation for the use of these drugs are not borne out by our experience. Only severe postconvulsive excitement states are a sufficient reason to inject $7\frac{1}{2}$ grains of sodium amytal intravenously. A less dangerous, though not quite reliable means of preventing postconvulsive excitements is the use of 4 or 5 cc. coramin given intravenously prior to ECT. This combination was first recommended by Fabing¹⁷ as a means to increase the effect of ECT in excitement states. This might have the same explanation as the seemingly better response of such conditions to metrazol treatment with its combined chemical and convulsive effect on the brain.

Fear of the treatment is no sufficient reason to use sodium amytal

routinely. In ordinary ECT, contrary to metrazol therapy, unpleasant sensations are absent. Yet, some fear is often expressed and connected with the idea of losing consciousness. More puzzling is a stronger fear reaction which takes place in some patients after several treatments. The patient usually gives no explanation for this ill-defined fear which seems to be related to his confusion. Some patients explain it with the belatedly remembered period of awakening from their previous treatments.

The organic reactions during ECT are not limited to memory impairment but, like all organic reactions, they show emotional changes. They can be distressing but they are never of long duration. Thorough psychological testing as well as psychiatric follow-ups have convincingly ruled out any permanent organic damage beyond the deteriorating effect by the psychosis as such. Likewise temporary is the electroencephalographic evidence of brain damage after ECT. This is in accordance with the absence of neuropathological evidence of irreversible brain damage. Pathological findings reported by some observers, were not confirmed in any of the numerous subsequent investigations. Organic psychotic reactions of manifold symptomatology which may occur even after very few treatments do not seem to have a neuropathological basis; they clear up without leaving any traces even if the point of deep organic dementia is reached which some clinicians produce purposely by giving 3 or 4 treatments daily in order to increase the therapeutic effect of ECT. We did not convince ourselves of the need for such accumulation of treatments but can confirm the harmlessness of this procedure regarding permanent damage.

The importance of ECT as a valuable tool in psychiatry is no longer under dispute among those who have ever applied it, even though the various shock treatments perhaps did not live up to early expectations. Many psychiatrists still reject ECT for reasons of principle without having any experience with it. Indiscriminate use of the treatment by unqualified men lends some weapon to those fighting it. Such indiscriminate use is easily promoted by the possibility of ambulatory treatment. Yet, ambulatory treatment as such is not objectionable and will have an increasingly important place in our fight against mental illness. It can be given in clinics as well as in offices. Although the larger part of the author's personal experience derived from hospital patients, no complications were ever encountered that could not be

dealt with just as well in an office. The disadvantages of ambulatory treatment are more than compensated by its social importance. Respiratory difficulties which are the only true emergencies can be dealt with in any office well equipped for this particular type of treatment. More unpleasant for the physician than for the patient are the post-convulsive excitement states for which the psychiatrist giving ECT should be prepared with adequate personnel and measures for temporary restraint until such patients regain full consciousness. A disadvantage of both, clinic and office treatment, is that the patient must be taken care of by his family during the confusional state frequently caused by ECT. More serious is the difficulty to give a sufficient number of treatments to ambulatory patients. The patient and his family are not easily convinced that often treatment has to be continued after the patient is symptom free. This, and the occasional activation of symptoms are the reason why schizophrenics who require a long course of treatments, should rather be hospitalized. Exceptions are chronic cases where not more than a symptomatic effect of a few treatments is planned, and those where treatments are given chiefly as a prognostic test to determine how promising a full hospital course of any type of therapy would still be.

In view of the many problems involved in ambulatory treatment, it should be requested that only psychiatrists with special experience in this field should be allowed to give office treatment, that one or two specially trained nurses are available, that the treatment not be given to patients unaccompanied by relatives, and that the patient be kept in the office for at least one hour after the treatment. Other requirements are that the family be fully informed of the fact that patients under ECT have to be watched constantly at home for approximately one week after the last treatment until the confusion has cleared up, and finally that the psychiatrist giving the treatment should feel responsible for a follow-up of the patient and, if the patient requires hospitalization during the treatment, discuss with the hospital the continuity of the treatment.

Clinic facilities for ECT should be provided to an increasing extent in general hospitals and, more important, in state hospitals. This would eliminate the admission of patients whose symptoms can be removed with very few treatments such as depressions, and it would prevent readmissions of patients who had a full course of treatment in the

hospital but, after discharge, have a tendency to relapse. Such treatment, successfully applied in most English mental hospitals, would change the after-care clinics of institutions into active treatment centers and decrease the admission rate.

INDICATIONS

The main indications for ECT have been listed frequently. Yet, there is so much confusion and disagreement that they will be discussed here once more in an attempt to clarify some of the disputed points.

The value of ECT in the affective disorders is generally accepted. Its almost specific effect in clearing up depressions after 4 or less treatments is the most convincing proof that this somatic method in psychiatry is a therapeutic approach in the right direction. There are few better predictable therapeutic effects in medicine. Manic-depressive, involutional and old-age depressions react equally well. It is amazing to see most depressions of various depths and duration clear up with the same number of three to five treatments. One or two additional treatments are advisable, but there is little evidence that in depressions a longer course of treatment promises a more lasting effect. It is true that manic-depressive episodes recur whether treated or untreated, but the great value of ECT in these conditions cannot be questioned when we realize how much human suffering is prevented by shortening the episode. The safe prevention of suicides should be reemphasized, because we all know of instances where misrepresentation of the treatment in newspapers and motion pictures discourages patients and relatives from accepting the only treatment which prevents suicides in depressions. It is frequently overlooked that moderate depressions are a much greater suicidal risk than advanced cases with no initiative left. Delaying treatment in such cases is negligence. ECT as the treatment of choice in depressions belongs to those facts about psychiatry which the general practitioner should know because it is he who sees these patients when they begin to be sleepless, to lose weight and to complain of vague physical symptoms. In these patients general medical measures are of no avail including the endocrine substances which are still widely used in involutional depressions.

Contrary to depressions, manic episodes were often reported to be unresponsive to ECT. This is not so when one to three treatments are given on several subsequent days. Failures are often due to the wrong

diagnosis of certain schizophrenic syndromes as manic episodes. That depressed patients after ECT turn hypomanic is not infrequent, and often represents a short organic reaction which does not require further treatment. When a true manic episode follows a depression, renewed treatment is indicated. Manic-depressives who constantly change from elation to depression are poor candidates for ECT except for a symptomatic removal of the more acute psychotic manifestations. Preventive use of ECT once a month in manic-depressives was successfully tried by Geoghegan and Stevenson.¹⁸ Unfortunately, few patients are co-operative enough for such treatment.

In involutional melancholia 5 to 8 treatments are usually sufficient. Failures belong almost exclusively in the group of involutional psychoses of the paranoid type. They respond less well and need a much longer course of treatment. Their treatment prognosis often depends on the depressive component in their symptomatology.

Schizophrenia is the disease for which convulsive therapy as well as insulin coma treatment were originally introduced, and for several years, exclusively used. The spectacular results of ECT in the affective disorders discouraged psychiatrists regarding its application in schizophrenia. It is true that here the quick response to 4 or 5 electric shock treatments is often followed by a relapse, but routine application of 20 or more treatments even in cases of early improvement, makes results comparable to insulin therapy. Some workers feel that in paranoid schizophrenics insulin yields better results. More and more hospitals have replaced the difficult insulin method by ECT. We do not entirely agree with this attitude. In a disease where all treatments are still highly unsatisfactory, every approach should be used. The frequent competitive recommendation of the various shock treatments has to be replaced by an effort to supplement one method with the other.

Applied adequately, ECT gives 60 to 70 per cent good remissions during the first six months of illness in patients with acute onset. The remission rate remains satisfactory up to one year of illness but drops rapidly after one year, thus emphasizing that early treatment in schizophrenics is imperative. Figures are much lower in patients with insidious onset of the disease.

Of the subtypes of schizophrenia catatonic excitements respond best; next are acute paranoids. Catatonic stupors, wrongly considered

the best prospects for ECT, relapse frequently. The poorest results are obtained in hebephrenics. This is not surprising when we realize that the primary schizophrenic symptoms respond little to treatment, and that even patients with good results maintain some "scarring," such as reduced affectivity or some thinking disorders.

Complete failure is often encountered in "late" paranoids and similar syndromes in the middle age group, classified as paraphrenia. Also cases close to the rare group of true paranoia do not respond. Another group usually refractory to ECT is that of hypochondriasis in the older age bracket. These patients with bizarre physical complaints are usually treated a long time for physical ailments until the psychiatric origin of their complaints is recognized. They are often diagnosed as agitated depressions. They rather belong to the schizophrenic group, but respond less to ECT than most schizophrenics do.

The inadequacy of ECT in the treatment of schizophrenia explains that combinations with other treatments are frequently used. Combined ECT-insulin treatment is indispensable in schizophrenia in spite of the experience that patients who failed under intensive treatment with one shock method respond little to others. In combined convulsive-insulin therapy metrazol has not been entirely replaced by ECT. At the Psychiatric Institute we combine it with ECT without seeing any of the originally dreaded respiratory difficulties. The convulsion is given at the end of the hypoglycemic coma, and the coma is terminated immediately after the convulsion by means of a previously introduced nasal tube. Combination of ECT with fever therapy (Fuster¹⁹) is used in those countries where sulphur in oil and other fever producing preparations are considered valuable in the treatment of schizophrenia.

Since the introduction of lobotomy and other neurosurgical procedures it is important to establish when shock treatment in a schizophrenic should be given up. The still prevailing attitude to limit surgery to chronic cases of many years' duration, has to be revised. Our recommendation is to apply 20 to 40 shock treatments, and in case of failure, insulin in combination with convulsive therapy. This requires hardly more than six months, and surgery can be considered before one year of continuous sickness has elapsed.

The relationship between ECT and the psychosurgical procedures requires two more comments. A "prognostic electric shock test" is a useful tool in the selection of chronic schizophrenic patients for psy-

chosurgery. Such a test consisting of 3 or 4 convulsions removes temporarily the reversible part of a psychosis and will tell how far the patient's personality is still preserved under a psychotic syndrome. Thus, it may show whether an uncommunicative catatonic is completely empty or only blocked, and give important clues as to how far the patient's symptoms can still be removed by surgical procedures. Finally, postoperative ECT is sometimes useful in removing psychiatric manifestations uninfluenced by surgery.

A discussion on ECT in schizophrenia would be incomplete without stressing the importance maintenance treatment with one or two occasional ECT given whenever an incompletely improved patient begins to become worse. Such treatments keep many patients on a better level and may prevent readmissions. Applied in all chronic wards of mental hospitals such symptomatic treatment can do away with restraint, tube feeding, continuous baths and similar measures, and thereby completely change the looks of the "backwards" of our mental institutions. The effect on the morale of patients, relatives and the hospital personnel is a factor which cannot be overrated.

It is not generally recognized that ECT is of some value for the psychotic manifestations of certain organic conditions. In general paresis a few ECT remove mental symptoms prior to malaria or penicillin therapy, and, thus, facilitate the treatment of such patients in general hospitals where they would otherwise not be acceptable. Also residual symptoms after malaria or penicillin therapy respond well to ECT. Psychotic episodes in cases of Parkinson's disease or other neurological diseases respond equally well to ECT. In epilepsy psychotic manifestations such as clouded states which are often interrupted by spontaneous convulsions, respond well to artificial electrically induced seizures. Epilepsy is no contraindication for ECT, and it was shown that the convulsive threshold is temporarily raised after each preceding convulsion. Therefore, in patients with predictable convulsions as seen in menstrual epilepsy, artificial seizures can even be used to prevent spontaneous convulsions. This has little practical importance but it is another proof that the fear of epilepsy as an after-effect of ECT is unfounded.

A few rarer indications seen to have in common the blurring effect of ECT. Neurodermatitis and other itching skin conditions may heal when the urge for scratching is temporarily eliminated by a few con-

vulsions. Attacks of bronchial asthma often disappear while a patient is under ECT, but also an aggravation of asthma has been reported (Cohen and Holbrook²⁰). Withdrawal symptoms in morphine addicts can be eliminated by a few ECT.

The largest group of psychiatric patients not responsive to ECT is represented by psychoneurotics. Most criticism of ECT results from its indiscriminate use in the psychoneuroses. It cannot be emphasized enough that contrary to psychotics, some neurotics may be harmed by ECT. Anxiety, as the most frequent symptom in neurotics, is often aggravated. Many neurotics react badly to the memory impairment and complain of it long after psychological tests have shown that actually no impairment persists. Conversion symptoms sometimes disappear as they may do after any impressive treatment, but more often side-effects such as headache, muscle pain, and so on, are added to the patient's complaints. The only group of neurotics where ECT is indicated, are the reactive depressions. They respond as well as other depressions, but the neurosis from which the depression developed, remains subject to psychotherapy. Only few authors felt that ECT expedites psychotherapy in those psychoneurotics who seem rutted in their illness (Hamilton²¹).

The question of psychotherapy in all cases treated with ECT takes up much space in the literature but remains unsettled. The statement that ECT should be only used as an adjunct to psychotherapy has been reiterated in many papers, but no attempt has ever been made to compare series of ECT patients treated with and without simultaneous psychotherapy. It is unquestionable that the most favorable results in ECT were reported from large institutions where no psychotherapy was applied. The comparison of two series treated by us with the same technique, showed far more favorable results in the institutional material in spite of the lack of psychotherapy. This applies only to psychotics, while in psychoneurotics, if there is any indication for ECT, it can only be an adjunct to psychotherapy. Psychotherapists frequently request ECT from us to break through a patient's resistance. This can be done by using the organic blurring which is a side-effect of ECT, but it is of questionable value and not comparable to the curative effect of ECT in many psychoses. Our experience led us more and more to the conclusion that psychotherapeutic measures and shock treatments have mostly different indications and rarely overlap.

The reluctance on the part of some psychiatrists to apply ECT even in those cases where a favorable result is clearly predictable, is based primarily on theoretical objections. It is true that the shock treatments have no foundation in psychological theories; on the other hand, those thinking in organic terms, are as much at a loss to understand their action. As treating physicians we cannot wait for satisfactory theories. As psychiatry begins to enlarge its therapeutic armamentarium, we psychiatrists like other physicians will learn to select the right therapeutic techniques for the right type of patient. If this is done, ECT applied with discrimination, will be helpful in many psychiatric patients.

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THE MEDICAL, SOCIAL AND PUBLIC
HEALTH ASPECTS OF REHABILITATION*The Hermann M. Biggs Memorial Lecture**

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WHEN Dr. Hermann M. Biggs, whom we are meeting here to honor this evening, was born in Trumansburg, New York, on September 29, 1859, both the field of public health, for which he did so much, and the City of New York, which benefited principally from his pioneer efforts, were far from the complex structures they represent today.

An overgrown village, New York City, at that time, had just begun to push its way up the Island of Manhattan. The last house on Madison Avenue was then on Twenty-Seventh Street, and the new water reservoir on Murray Hill near Forty-Second Street had just been completed. There was no city sewage system, and the flood of poverty-stricken immigrants who squatted in crowded tenements near the docks, constituted a serious public health problem.

It was during this same period that Dr. Lemuel Shattuck of Boston, in his report of the Massachusetts Sanitary Commission, wrote the blue print for the modern concept of health organization in which public health is considered responsible for those health problems which, for their solution, require systematized social action.¹

The principles of public health and preventive medicine in this nation, however, did not originate with Dr. Biggs or Dr. Shattuck. As early as 1647, the Massachusetts Bay Colony set up quarantine regulations when news reached the colony of a "great mortality" in the West Indies. The first board of health in the nation was established in Petersburg, Virginia in 1780, and similar organizations were established in New York, Baltimore and Boston in the 1790's.²

At that time, until the concept of public health was widened by men like Dr. Biggs, who believed in a more positive approach, public health

* Given April 7, 1949 at the Stated Meeting of The New York Academy of Medicine.

was restricted largely to sanitary measures, quarantine, and the elimination of "public nuisances."

It was not until the introduction of the science of immunology by Pasteur and the application of this new knowledge that public health concepts were greatly broadened.

Today, we are once more standing on the threshold of a new concept which has, paradoxically, been forced upon us by medicine and public health through their success in reducing the incidence of death from acute, communicable disease, and producing the phenomena of an aging population. When Hermann M. Biggs was born in 1859, the average life expectancy in this country was forty years. When he was appointed the first general medical officer of the Department of Health of New York in 1901, it was forty-nine. This year, on the ninetieth anniversary of his birth, it is 66.5.

What are the medical and public health implications of this increasing age level of the population? First, as people become older, their medical needs change, and they demand more medical service. In 1940, the 26.5 per cent of the nation's population over 45 required over half of the nation's medical care. By 1980, it is expected that the number of persons over 45 will constitute nearly half of the population.³ Today, we are busily studying and discussing the needs and best plans for increasing and distributing medical services, yet the growing age level of the population indicates that by 1980 we may need nearly double the amount of medical service that is available today.

Secondly, lacking specific measures in the cure of many of the chronic diseases, medicine must look to rehabilitation to teach those afflicted by chronic disability to live and to work as effectively as possible with what they have left. Until medicine finds specific answers to the problems of the diseases of the heart and circulation, rheumatic fever and arthritis, cerebral palsy, multiple sclerosis, poliomyelitis and the other crippling diseases, we must utilize the techniques of physical rehabilitation, psychology, social service and the other allied ancillary specialties of rehabilitation to teach the disabled to live within the limits of their disabilities but to the hilt of their capabilities.

In thinking of the disabled, the average citizen is inclined to think of disabled veterans, yet the extent of physical disability among our civilian population is far greater. For example, the number of persons permanently disabled in farm accidents in 1945 was four times greater

than the number of servicemen permanently disabled in the bloody assault on Iwo Jima. Ignoring the vast number of persons who suffer disabilities resulting from disease, each year in this country nearly 50 per cent more persons are permanently disabled from accidents alone than there were American servicemen disabled as a result of combat during the entire four years of the war. Added to these are the 8,000,000 to 9,000,000 persons who suffer from disease of the heart and circulation, the 6,850,000 from rheumatism and arthritis, the 300,000 from cerebral palsy and a probable like number from the residual effects of poliomyelitis, the 1,000,000 known and additional 1,000,000 unknown cases of diabetes mellitus, the half million to one and one-half million persons with epilepsy, the 400,000 persons who have undergone major amputations, and the millions who suffer from disorders of vision, hearing and speech.⁴ These are the numbers, but they cannot tell the story of pain, anxiety, suffering and all of the difficult secondary problems that disease and disability leave in their wake. Aside from the pain and tearing personal and family anguish, the economic costs of disease and disability are staggering.

Until we find the etiology and treatment for the chronic diseases producing disability, we can expect, as the population ages, that the extent of physical disability in this nation will progressively increase. Since chronic disease is usually non-reportable, it is difficult to find reliable statistics on its extent. Although a census of such conditions has been proposed on several occasions, there has never been a complete survey of the extent of disability in this country. The most comprehensive source of information at present is the National Health Survey, conducted by the United States Public Health Service in 1935-1936.⁵ In this survey, 800,000 families in eighty-three cities and twenty-three rural areas of nineteen states were studied. The reliability of this study has been demonstrated in other selective samples on the extent of chronic disease and crippling conditions, and although results are not strictly comparable due to different methods of enumeration,^{6,7,8,9} they bear out the fact that the National Health Survey is probably the best source available for such statistics, although later studies indicate that its results are probably conservative. It was this study that reported there were at that time some 23,000,000 persons in the United States who were handicapped to some extent by disease, accident, maladjustment or former wars. In a more recent study in New Haven conducted

by the School of Public Health of the Yale University College of Medicine it was found that 121 persons for each 1,000 in the population suffered from chronic illness, and that one-third of this number were totally disabled and one-third below twenty-five years of age.¹⁰

One of our great medical needs today is for the provision of total treatment of chronically ill patients in terms of the every-day problems of living which they face. Many such patients cannot be rehabilitated to the extent of employability, but a great percentage can be rehabilitated to the point of sufficient self-care so that they can live independent, dignified and happy lives at home, requiring a minimum of aid from other members of the family.

There was, at the war's end, some skepticism of the value of medical rehabilitation in the Veterans Administration hospitals for veterans of World War I, and those of the Regular Army who suffered from chronic illness and long-standing disabilities. Some physicians feared that young veterans of World War II would soon lose ambition, initiative and a desire for personal independence through association with older veterans who had developed "hospitalitis" as a result of boredom, frustration and hopelessness. In the veterans hospitals where comprehensive, dynamic rehabilitation programs are now in operation, the results have been not only revealing but encouraging.

Illustrative of the results obtained in the Physical Medicine Rehabilitation program in the Veterans Administration is a study of 130 chronic neurologic patients in one hospital, all but two of whom were World War I veterans, and many of whom had not been out of bed in ten years.¹¹ After nine months of rehabilitation, twenty-five had left the hospital and were employed; forty others had been discharged to their homes capable of light work, and, of those remaining, thirty were ambulatory and undergoing advanced rehabilitation, and twenty-five were capable of some self-care. All but 10 of the group had shown some worthwhile permanent improvement. With a five-year life expectancy of these patients, and a per patient day hospitalization cost of over \$12, rehabilitation of this one group has saved the government, and eventually the taxpayer, over \$1,125,000. It would seem logical that a similar program for the civilian chronically ill would result in comparative savings.

In another study at the Veterans Administration Hospital at Manhattan Beach, Brooklyn, through rehabilitation, seventy-four of a group

of 126 patients suffering from such diseases as arthritis, multiple sclerosis, Buerger's, Parkinson's and heart disease and various forms of paralysis, have been discharged from the hospital and are now at home taking care of themselves.¹² All but thirteen of the original 126 patients have recovered all or part of their ability for self-care. At the beginning of this study, eighty-three of these veterans were classified as "completely hopeless," but forty-nine of this group have been rehabilitated to the point of complete independence, and the remainder are capable of self-care.

The importance of dynamic therapeutics in the treatment of chronic illness in the Veterans Administration is readily apparent when we realize that the approximately twenty million veterans in this country represents a static population that is increasing in age daily. As pointed out in the Report of the Administrator of Veterans Affairs for the fiscal year 1948, there will be almost as many World War II veterans alive (3,800,000) at the turn of the century, 2000, as there were World War I veterans (3,727,000) in mid-1948.¹³ The average age of the World War II veterans then, however, will be nearly 78 years, compared with an average in mid-1948 of less than fifty-five for World War I veterans, and seventy-two for Spanish-American War veterans.

Both the Veterans Administration and some civilian hospitals have demonstrated that rehabilitation to the point of self-care and even to full or limited employment is possible for many of the chronically ill who have been hospitalized over long periods. Yet, in most of our civilian hospitals, the patient receives few services of this type. Hospitals complain that the chronically ill are responsible for their overcrowding, but they do little to provide the retraining services that will permit many patients to leave the hospital.

The hospital of today is being recognized more and more as the focal point in public health activities. With the changing demands being placed upon it because of the growing incidence of chronic disease and disability, it must also play a more important role in the rehabilitation of patients. Hospitals in the past have concentrated almost solely upon the definitive aspects of medicine and surgery. If the hospital is to meet the changing health needs of the public, it must assume greater responsibility for all three phases of health—prevention, definitive treatment and rehabilitation. As Bayne-Jones has said, "... they must become increasingly houses of prevention instead

of houses of pity."¹⁴ for the problems of chronic disease can be met only by the creation and utilization of abilities, rather than merely the building of facilities.

Although it would seem logical that medical rehabilitation would be an important service in every civilian hospital, there has been little or no attempt, until recently, to establish such programs in civilian hospitals. Of the 1,468,714 hospital beds in the United States in 1946, 44 per cent were in general hospitals, but these 641,331 beds cared for 92 per cent of all patients.¹⁵ Rehabilitation, in varying degrees, has been available in some tuberculosis, mental and other specialized hospitals, but little provision has been made for a dynamic rehabilitation program for the over 14,000,000 persons who are patients in general hospitals each year.

The Hospital Council of Greater New York has recommended that bed requirements for rehabilitation and convalescent care be placed at one bed per every one thousand population.¹⁶ This would mean that approximately 20 per cent of the beds in general hospitals would be utilized for this purpose. It was felt by the Council that the allocation of this number of beds and the introduction of a dynamic rehabilitation program would decrease hospital days, provide facilities for the evaluation and training of convalescent and chronically ill and disabled patients, and would help provide a program of total medical care.

Medical examination, x-ray and the usual hospital routines are not enough to meet the problems of the disabled persons. A diversified but integrated program must be developed for such patients on the basis of their needs in meeting day-to-day life situations. They must be provided with a program for training to teach them to utilize their residual abilities to the maximum. Patients must be tested and then trained in the activities of daily living; the simple things, such as turning over in bed, dressing and undressing, applying and removing braces, getting from the bed to the wheelchair or the standing position. These are every-day things, but they are the foundation of self-care and physical independence.

Illustrative of such cases is that of TF, a young lawyer who was admitted to the Rehabilitation and Physical Medicine Service at Bellevue Hospital in 1946. Paralyzed in all four extremities and the abdominal muscles as a result of poliomyelitis in 1940, this patient was entirely

helpless. His physical capacities were limited to the ability to grasp to some extent with his hands, and partially to move his fingers. His hand function was estimated at 15 per cent of normal.

He was 37 years old, and had spent a year in general hospitals and four years in various specialized hospitals. He came to Bellevue Hospital from a hospital for incurables. Although little could be done for this patient in the way of physical restoration, his vision, speech and mental ability were not affected, and it appeared that with the proper mechanical devices to meet some of the basic problems of daily living, he could return to the practice of law. With a cock-up splint for the wrist, and a rotary splint for the forearm, he was taught to feed himself. With a toggle switch on a French-type telephone mounted on a stand, he could signal the operator and thereby communicate by telephone. He learned to type with a remote control electric typewriter that could be operated with a minimum of strength and motion. With the combined efforts of the rehabilitation team of the doctor, the nurse, the therapists, volunteers and the most important member of the team—the patient himself—he learned within seven weeks to turn over in bed unaided. This meant that he did not need an attendant at night. He was discharged last July, and since that time has been living in mid-Manhattan practicing law.

Hospital programs alone, however, are not enough. If we are to meet the needs of the disabled and chronically ill, we must have a broad community program of dispersal after discharge from the hospital. The hospital, of course, is the focal point, the sorting station and the training ground, for just as satisfactory job placement is the capstone of any successful program of services to the handicapped, medical rehabilitation, starting at the earliest possible moment following acute illness or injury is the foundation, for all subsequent rehabilitation processes are built upon the residual physical disability which medical services cannot eliminate.

The end of rehabilitation for some patients leaving the hospital is *full employment*, for in many instances the disability can be eliminated or the patient can be rehabilitated to the point that he is not vocationally handicapped. An example of such cases is that of a miner recently sent to New York for rehabilitation under the auspices of the Welfare and Retirement Fund of the United Mine Workers of America. For five years this patient had had a total paralysis of one of the upper extremi-

ities which came on after an injury in the mines. The nerve had healed completely, but during the long healing process, the arm had become alienated. Electrical stimulation demonstrated to him that the hand was functional. After three days of therapy, the patient had a 90 per cent return of function and only needed continuing treatment to restore the atrophied muscles to their normal strength, in order to return to his old job.

The great majority of those patients who are permanently disabled are not vocationally handicapped if *selective placement* procedures are used, in which an analysis is made of the physical capacities of the individual and then are matched to the physical demands of the job. Just as there are powerful forces of physiological compensation in the case of disease or injury, it is possible, through retraining, for the remaining physical capacities of the disabled individual to be utilized vocationally. With the paraplegic patient placed in a position which requires strength in the muscles of the shoulder girdle and upper extremities, the blind person in a position which requires finger dexterity and aural acuity rather than vision, and the deaf person in a working atmosphere of noise and confusion, objective studies have shown they are far more reliable, efficient and safe employees than the able-bodied.

For those persons whose physical disabilities are so great that they cannot work in normal industry even with selective placement, we must have a series of *sheltered workshops*. Here in New York and throughout the nation, we have a number of pioneer institutions such as the Institute for the Crippled and Disabled, the Division of the Handicapped of the Brooklyn Bureau of Social Service, the Goodwill Industries, and others who have demonstrated the physical, psychological and social values of permitting any person regardless of the severity of his disability to gain dignity which comes from productivity.

For those persons whose disabilities will not permit them to travel to and from a sheltered environment, we must provide programs of *home care, housekeeping services, and industrial homework*. As demonstrated by Jensen's work at Rochester, similar programs in Syracuse, and the outstanding program developed by Bluestone and his associates at Montefiore Hospital here in New York, the provision of home medical care programs supplemented by adequate social service and visiting housekeeping service can reduce the financial and professional strain upon our hospitals and give the patient a more satisfying life

within the family environment. Added to this there should be a program of industrial home work both for the monetary and psychological benefits it can bring to patients.

One of our most neglected groups in the chronic degenerative disease category of patients has been the *senile psychotics*. They have usually been placed in the almshouse or county institution along with individuals of all ages and of normal mentality, or have been sent to state institutions for the insane where often, because of the crowded conditions, they have been placed with severely disturbed psychotics.

How a community can meet the needs of this particular group has been demonstrated in Vancouver, B. C., where a number of small, standardized, economically-built 100 bed units for their care have been placed in centers of population. The doctors in each community have assumed the medical responsibility, and mature, motherly type practical nurses have been selected for patient care. Such units, strategically placed, allow the patient to maintain contact with his former environment and have visits with his old friends and family. Through such plans, optimum results may be obtained at minimum cost.

In our failure to utilize "work therapy" with institutional patients suffering from chronic disease and physical disability, we have neglected one of the most valuable tools in the management of this group of patients. All who have gone through a custodial institution have noted the apathy and hopelessness of most residents. There are always a few however, who are bright and active. They are the patients who have volunteered or have been assigned to tasks within their physical capacities.

The use of selective placement can be used in such institutions as well as in industry. Even though their capacities may be limited, the great majority of the residents of public homes can do some tasks about the home. For some it may be only simple housekeeping assistance; others may have the ability and experience to assume greater responsibilities. Such jobs should carry regular compensation, even though it be small, for there is no greater satisfaction than that which comes through earning. In many homes, it would be possible to provide sheltered workshop facilities where residents could do either industrial home work or necessary services for the community operating the home. Like work for the homebound, such plans require both imagination and close supervision to prevent exploitation, but they would pay

tremendous dividends by providing a purpose in life for many patients.

Both the same therapeutic techniques and community dispersal agents should be utilized in the treatment of the *psychoneurotic* patient. Experience in the military services and the Veterans Administration have shown the value of well-planned programs of physical activity, work therapy, recreation, social services, vocational guidance and education, to be invaluable as adjunctives to definitive psychiatric treatment. With the introduction of such programs into Veterans Administration Hospitals, the use of restraints and of sedatives has dropped remarkably, and today the Veterans Administration for the first time in its history is discharging more neuropsychiatric patients than it is admitting. This, of course, is not due to their adjunctive activity program alone, but as a result of a dynamic total-approach concept of psychiatry of which adjunctive activity is an integral part.

Similarly, if we are to have an effective program for the *tuberculous*, emphasis must be placed on rehabilitation as well as upon case finding and definitive treatment. Too frequently, the arrested tuberculous patient is discharged from the sanatorium unable to cope with the realities of life, such as finding suitable employment and housing, meeting his family responsibilities, and learning to live within the limits of his disability. Rehabilitation within the tuberculosis sanatorium not only helps keep the patient psychologically and socially adjusted so that he will remain under treatment, but it helps prepare him for the problems he will face upon discharge. Adequate rehabilitation within the hospital and post-hospital programs of supervised work tolerance and necessary vocational training are as essential to tuberculosis control and total treatment as mass chest x-ray surveys and chest surgery.

With the introduction of rehabilitation programs in general hospitals, increased facilities for convalescent care and home care programs of medical, social, visiting nurse and visiting housekeeping services, many of the aged and chronically ill will not need to seek admittance to public homes. Many present residents could be restored either to employment, selective placement, sheltered workshop employment, or self-care within the home. But in order to accomplish this, there must be a complete program for evaluation and training within the hospital.

Age plus physical disability will prevent many chronically ill persons from returning to employment. Vocational placement, however, is not the only valid goal of rehabilitation. The factors of self-care and

ability to do productive work while still living in a hospital, home or other institution are also valid objectives. They are valid medically and socially for their effect on the well-being of the person, and economically, in that personnel and operating costs of the institutions or the patient's home are thereby reduced.

The physician has always been interested in the total welfare of his patient. Prior to World War II, however, the great majority of the medical profession looked upon rehabilitation as an extra-curricular activity of medicine, something dealing with social work and vocational training, but for which he had little concern and held but few medical implications. Today, that trend is being reversed, and although there are still many physicians who are unfamiliar with the aims and procedures of rehabilitation (in 1946 only 3 per cent of the new cases referred to state rehabilitation agencies and commissions for the blind were from physicians), more and more, medicine is beginning to recognize that medical care is not complete until the patient has been trained to live and to work with what he has left.

Smith and Evans define public health as all medicine that seeks to alter or better the patient's physiological status. There are two reasons why rehabilitation must be considered a part of public health. First, the rehabilitation program of this country nationally will rise or fall in proportion to its integration into the total public health program. Case finding, post-hospital supervision, the full utilization of all community resources and the other many facets of public health are essential to an integrated community rehabilitation program.

Second, the public health service must assume this responsibility, for, ironically, such services helped create the crisis we now face, a crisis created by sewage systems and the control of infectious disease, by nutrition and health education, by sanitary measures and food inspection, by everything that has been done to provide better health for the American people. It has made people live longer; long enough so that they eventually acquire chronic disease and its resultant physical disability. We are in a paradoxical situation, for, with every advance in medicine and public health, we add to the responsibility and the problems of rehabilitation.

The medical and health crisis which we face in this country today is not one of sanitation, vaccination or water purification; it does not involve typhus, malaria, venereal disease and the other problems which

can be brought under the focus of the microscope and within the orbit of our modern therapeutic knowledge. The patterns are established and the tools are available to meet these problems. Our present-day crisis is a slowly advancing, insidious, chronic epidemic, progressing just as slowly and surely as a serpigenous ulcer. As the years progress, it will cease to be epidemic and will become endemic, our self-created endemic of chronic disease and an aging population. Just as public health solved the epidemics created by bacteria, we can meet this epidemic of chronic disability only by creating new weapons and new understanding, taking both the medical and social responsibility for this Frankensteinian phenomena we have created. As Bortz so aptly summarized, "The society which fosters research to save human life cannot escape the responsibility for the life thus extended. It is for science not only to add years to life, but, more important, to add life to the years." This is our responsibility.

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CONCERNING VOLUNTARY AND INVOLUNTARY MOVEMENTS*

THE ROLE OF CORTICO-SPINAL AND SUBCORTICO-
SPINAL MECHANISMS WITH A CONCEPT AS TO
THE ORIGIN OF MOVEMENTS

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THE CLINICIAN is at times confronted with perplexing problems, as he attempts to correlate the presenting symptomatology with data obtained from anatomicophysiological sources. In hemiplegia with spasticity of the involved extremities, he expects to demonstrate the Babinski sign, to find the abdominal reflexes absent and the tendon reflexes hyperactive. He is no longer surprised if tone is diminished rather than increased and realizes that this is especially so when the postrolandic area is the seat of pathology with resulting sensory impairment. He is aware also that a lesion of area 4 may result in decreased reflexes and no spasticity. He is not, however, as easily reconciled when in the spastic lower extremity of the hemiplegic, he cannot elicit the Babinski sign, or when a patient with amyotrophic lateral sclerosis presents hyperreflexia in all four extremities, spasticity in the lower limbs with bilateral Babinski; and yet the abdominal reflexes are brisk. He appreciates the relationship between the pyramidal and extra-pyramidal systems; that when a patient with paralysis agitans becomes hemiplegic, the tremors usually cease in the paralyzed limbs, and that as motor power is restored in some hemiplegic patients, they may then manifest abnormal involuntary movements. Numerous publications have added to this perplexity. Recently, a case was reported with lesions of the pallidum, substantia nigra and pyramidal tracts. The author was quite concerned because "despite the involvement of the pyramidal tracts, rigidity and tremor did not disappear." Another author describes a case with extensive

* Read before a combined meeting of the New York Neurological Society and the Section on Neurology and Psychiatry, The New York Academy of Medicine, May 11, 1948. From the Neurological Service Kings County Hospital.

atrophy of the frontal lobe and atrophy of the caudate nucleus, and wonders why there were no abnormal movements.

The motor system includes all movements produced by contractions of muscles. The neural mechanisms concerned with movements and posture consist of the lower and upper motor neurons. In the organization of the lower motor neurons, the cells of origin lie in the anterior horns of the spinal cord and in corresponding nuclei in the brain stem. From these cells, impulses pass to the muscles through ventral roots, peripheral nerves and cranial nerves. The organization of the upper motor neurons is, however, quite complex and has not been satisfactorily clarified. Two main systems have been described, the cortico-spinal or pyramidal system; with the cells of origin in the motor cortex and the efferent pathway in the pyramidal tract, and an extra-pyramidal system with efferent fibers from centers in the brain stem and basal ganglia.

In living creatures in which a central neuraxis can be recognized, the oldest motor centers are in the spinal cord. From the viewpoint of phylogeny, the lower motor neuron from anterior horn cell to end organ is the original, the simplest unit of motor activity. For lower animals, such as birds, reptilia and fishes, the highest motor center, their upper motor neuron, is the corpus striatum. The oldest part of this, the paleostriatum obtains in fishes, whereas in reptilia and birds, there has developed the putamen caudate complex, the neostriatum.

Mammals with intact basal ganglia but with cerebral cortex removed, can walk or perform all ordinary activities. They lack initiative and have few, if any, conditioned reflexes. Such animals go about instinctively; there is no direction and certainly no planning in their performances.

These subcortical centers seemingly control all motor activities in animals with a rudimentary cerebral cortex. As the cerebral cortex evolved in higher animals, many of the functions of the basal ganglia were taken over by it. The cortex, has, however, not replaced the basal ganglia, but their combined functions have become amalgamated into a more comprehensive motor mechanism. Normally then both the old and the new motor systems appear to coöperate. They are not antagonistic. The efficiency of the one requires the collaboration of the other. There is a fusion of the two motor systems functioning harmoniously.

When man assumed the erect posture and the forelimbs no longer were needed for walking, the cerebral cortex attained its greatest development. The big toe became the largest of the toes and acted as the fulcrum in support of physical erectness. Man now walked on the sole instead of the outer border of the foot. However, walking on his hind legs alone did not require the elaboration of the motor cortex. The subcortical centers still were in control of all routine motor activities. The frontal lobe evolved when the forelimbs developed the ability to grasp. Until then, the animal had few if any conditioned reflexes and all activities were instinctively induced. The animal now realized that grasping a weapon gave him physical superiority over enemies who had previously dominated him. He accordingly now added planning and premeditation to all actions and there resulted the dawn of the higher consciousness, that kind of consciousness which we human folk enjoy. There are varieties of movement where the degree of consciousness is an important factor, but there are other classes of movement which appear volitional yet are entirely independent of consciousness. Simple reflexes are constant and usually invariable but may be modified or even suppressed by other reflexes or by influences of higher levels of the nervous system. Functions like righting the body when equilibrium is threatened are reflexes mediated at the brain stem level. Voluntary movements are more complex and more variable. They are initiated by will and are deliberate acts. They may be planned or premeditated, but may also result from repetition of past experiences or may be acquired by learning. Such highly differentiated voluntary movements are dependent on the activity of the cerebral cortex. However, the initiation and execution of fine and skilled voluntary movements by the motor cortex require a normally functioning subcortical system. The cortex may modify or suppress subcortical activities or utilize all or part of these subcortical activities for the execution of its own purposes.

Thus the frontal lobe evolved, not as a locomotor system, but to make possible newer functions, refined unilateral movements, dexterity, the planning and premeditation of actions, the element of deliberation, volition or intention. Obviously, the newer muscle or bony postural alterations are represented in the new neural organization, the motor cortex. In the quadrupedal mammal with the basal ganglia as the dominant motor neural apparatus, the big toe posture is dorsiflexion. With

the assumption of erect posture, the necessary big toe posture is plantar flexion, maintained by the newer motor cortex. Removal of the influence of the motor cortex or its efferent pyramidal tract permits the older subcortical control to return and we have the Babinski toe sign.¹ Similarly, removal of pyramidal tract control results in return to the older postures of the foot (*pes equino varus*) and the flexed hand, so common in hemiplegia.

Until recent years, the designations cortico-spinal tract and pyramidal tract were synonymous and applied to all the fibers descending from the cerebral cortex to the spinal cord. In this respect, it was believed that interruption of the pyramidal tract resulted in impairment of voluntary motor power causing paralysis; removal of inhibition of tonus distribution to the muscles resulting in spasticity and of the tendon reflexes, causing hyperreflexia; the superficial reflexes lost their innervation and could not be elicited and the Babinski toe sign appeared.

Von Monokow² and Swank³ demonstrated the presence of fibers in the medullary pyramid that did not originate in the cortex. Lassek and Rasmussen⁴ by silver technique, demonstrated in the human medullary pyramid unmyelinated as well as myelinated fibers; that the myelinated fibers constitute 61 per cent of the pyramid, but that only about 10 per cent of these make up the pyramidal tract. Additional studies by Mettler,^{5,6} Levin and Bradford,⁷ Verhaart and Kennard⁸ and others indicate that half of all the fibers in the pyramids are cortico-spinal and arise from the precentral gyrus and the parietal lobe. The origin of the remaining 50 per cent of the fibers in the pyramids is not certain and they should not be referred to as cortico-spinal or pyramidal.

It seems evident then, that in hemiplegia with spastic paralysis, hyperreflexia, absent superficial reflexes and the Babinski sign, in addition to the pyramidal tract, fiber pathways other than those originating in the motor cortex are involved. The only functions affected that seem truly cortical are voluntary motor power, and the removal of the plantar flexion response of the big toe resulting in the Babinski sign. The superficial reflexes may have their synapse in the cortex or subcortex. The inhibition or regulation of tendon reflexes and of tonus are not functions of the motor cortex, but depend on influx of afferent impulses through the sensorium and subcortical structures. The clinical

picture of spastic hemiplegia then is due to pathology of a number of fiber tracts, amongst them the cortico-spinal or pyramidal tract and other subcortico-spinal tracts, all converging on the anterior horn cells in their common interest, the production of the forms of normal motor activity possessed by man. Destructive pathological lesions such as occur in vascular disease may affect all these fiber tracts, whereas other types of pathology such as amyotrophic lateral sclerosis may be more selective and interrupt some of the fibers, yet permitting others to function normally. Thus the abdominal reflexes may be present despite spastic paralysis with Babinski and hyperreflexia.

Syndromes including abnormal involuntary movements have for many years created much interest and perplexity. Not long ago, many of them were regarded as of psychogenic origin. The clinician has observed, analyzed and described the numerous variations. There is little remaining conflict as to these described entities. These movements have been grouped according to their rhythm, amplitude and timing and there is seldom serious disagreement in the designations so long as these criteria are maintained. It is only when attempts are made to correlate these movements with anatomic, pathologic or physiologic data, that pitfalls arise. It has been puzzling to understand the mechanism which halts many of these movements during sleep, whereas others such as convulsive seizures occur in sleep. Similarly, much debate has ensued when, as a result of animal experimentation, it has not been possible to reproduce the type of movements observed in the human clinical syndromes.

In the main, the mechanisms responsible for the appearance of involuntary movements in clinical syndromes of the basal ganglia, have not been definitely established. From a critical analysis of the available data arising from clinical pathologic and physiologic studies, one must conclude that no final statement can be made concerning the functions of the striatum, pallidum and the related extra-pyramidal structures.

Many opposing theories have been formulated as to the role played by various components of the basal ganglia, cortical or other subcortical structures and their connecting pathways in the production of the dyskinesiae. Involuntary movements have been regarded by some authors as due to irritative lesions. Others have maintained that the pathologic lesions release other centers and thus permit the movements to appear. No such centers have been identified; certainly no stimulation

of intracranial structures has resulted in reproduction of any abnormal involuntary movements comparable with those present in disease of the basal ganglia. On the contrary, it is now stated that stimulation of the striatum produces inhibition of spontaneous movements emanating from the cortex. The globus pallidus had been regarded as inexcitable but more recent data would seem to indicate that the pallidum has a positive motor mechanism and that stimulation of it results in associated movement patterns involving the larger muscle masses (Mettler⁹).

Obviously, this positive motor phenomenon emanating from stimulation of the pallidum cannot be compared with the alternating tremor of Parkinsonism. Similarly, no absolute evidence is recorded suggesting that stimulation of any of the other basal ganglia structures has resulted in reproduction of the type of abnormal movements present in disease of these nuclei in humans. One may conclude then, that it has not been possible to reproduce by stimulation experiments, any of the dyskinesiae present in clinical syndromes of the basal ganglia. Such clinical syndromes occur only when the functions of these structures are in abeyance, due to destructive lesions.

Convulsive seizures may also be regarded as abnormal involuntary movements. They result from disturbed function of the cerebral cortex. It matters not whether the pathology is of the cortex itself or if the cortex is adversely influenced by pathology elsewhere or by metabolic or biochemical abnormalities in any portion of the body. These convulsive seizures differ from basal ganglia movements in two extremely important respects. Convulsive seizures occur with cortical lesions and can be reproduced by experimental stimulation of the cortex. Convulsive seizures occur during sleep whereas basal ganglia movements cease when the patient is asleep. Thus the only type of abnormal involuntary movement that can be reproduced by experimental stimulation, is the convulsive seizure which originates from the cerebral cortex but is not abolished by sleep.

If basal ganglia type of abnormal involuntary movements can not be reproduced by experimental stimulation of any part of the central nervous system, we must look elsewhere for their origin. Seemingly, these movements are abolished when consciousness is interrupted and recur immediately when consciousness is restored. The stimuli, therefore, seemingly enter through the sensorium, for when the curtain of consciousness is lowered, they are halted and do not then stream into

the organism. Whenever and wherever they enter the organism, these varying forms of molecular displacements traverse the ascending pathways. However, before they can reach the descending cortico- or subcortico-spinal pathways through which all motor impulses must pass to reach the final common motor pathway, important physiologic alterations take place. If this were not so, all animal life would appear in a state of disorder and unrest similar to that observed in the universe of inanimate objects and to which has been applied the designation "Brownian movement." These basal ganglia nuclear masses then alter, check, inhibit, divert, synchronize or neutralize. They modify the stream of these molecular displacements so that cortico- and subcortico-spinal pathways then transmit to the lower motor neuron, influences which result in the normal synchronized motor functions present in all animal life. When any of these basal ganglia are unable to function normally, there then passes through them on to and down through the descending motor pathways, those original unaltered molecular displacements which then produce in the musculature, the patterns of abnormal involuntary movements and tonus alterations which result in the clinical syndromes, the dyskinesiae that have been regarded as typical of basal ganglia disease.

Finally, unusual emotional factors such as fright and panic, often produce restlessness, tremors and other hyperkinetic phenomena. It would seem as though by suddenly overwhelming the resources of these basal ganglia structures, some of the entering molecular displacement patterns pass through unaltered into the descending motor pathways so that normal individuals may then manifest abnormal involuntary movements though there is no actual pathology in any portion of the nervous system.

DISCUSSION

The lower motor neuron or final common motor pathway to the muscles receives varying types of influences from the higher centers in the brain. Many of these have their origin from subcortical centers whereas others are cortically induced. The subcortical areas concerned with motor activities are way stations through which many of the stimuli necessary for the performance of motor functions pass. These subcortical areas influence or modulate the stream of motor impulses. Nothing originates or is initiated in these subcortical structures. Simi-

larly, it is probable that the motor cortex has been evolved as a higher replica of these subcortical centers. From motor cortex, impulses arise and flow through the pyramidal tract to exert an influence on the lower motor neuron system. Whether such impulses can actually be initiated spontaneously in the motor cortex is problematic. We know that the cortex can be induced to initiate a motor impulse by electric stimulation. In this respect, it differs from the subcortical areas where electric stimulation has as yet not reproduced the type of movements observed clinically in destructive lesions of these areas. It seems, therefore, that in the normal human, impulses do not start in the motor cortex unless stimulated or influenced by afferent impulses from the postrolandic cortex or from subcortical structures. It would appear that all areas of the brain are dependent for the initiation of their activities on the influx of stimuli which enter the body through the sensorium.

A destructive lesion of the motor cortex results in cessation of a motor function, not of individual muscles but of groups of muscles participating in an act requiring dexterity or finer movements and which are under the control of the will or are planned or premeditated. Pathologic stimulation of such a cortical area may produce excess movement of the involved muscle groups (Jacksonian fit). All activities of the subcortical areas, as well as the postrolandic sensory cortex and most likely all areas of the cortex which receive afferent impressions, converge on the motor cortex and the resultant effects appear in the efferent pathways and are conveyed to the anterior horn cells. However, in the human, it is probable that if the cortico-spinal pathways are interrupted, no influences from the higher centers reach the anterior horn cells and there is no motor power, the affected part is paralyzed.

Abnormal involuntary movements such as chorea, athetosis and alternating passive tremors occur in patients in whom post mortem studies have revealed pathology in the subcortical structures, pallidum and substantia nigra in patients with tremor, and caudate and putamen in those having choreo-athetoid movements. Accompanying such movements there is usually some tonus alteration in the affected muscles. It is of more than passing interest that it has not been possible to reproduce any of these dyskinetic phenomena by electric stimulation of these nuclear masses. Though definite fiber pathways connecting these basal nuclei with the cortex have not been completely and accurately charted, sufficient data are at hand to warrant the belief that there are afferent as

well as efferent projection systems connecting the two motor systems so that they can collaborate in the production of normal motor activities. Lesions of these basal ganglia result in abnormal involuntary movements when the main efferent motor pathway from cortex to anterior horn cell is able to convey impulses. Often post mortem study of the brain in cases of hemiplegia reveals in addition to the lesion of the internal capsule, extensive pathology of the basal ganglia, yet during the entire illness there were no abnormal involuntary movements. Such patients, because of the basal ganglia changes, would have manifested dyskinetic phenomena if the cortico-spinal tract had not also been diseased. All surgical measures for relief of tremor in Parkinsonism owe whatever success is achieved to this requisite, that the cortico-spinal tract must function if pathology in the basal ganglia is to result in tremor or choreo-athetoid movements. Whether the surgeon excises the cortex (Bucy¹⁰), or interrupts the fibers in the anterior limb of the internal capsule (Browder¹¹), or sections the dorso-lateral column in the spinal cord (Putnam¹²), the flow of efferent impulses through the cortico-spinal pathway is interrupted. Obviously the surgeons do not destroy all the efferent fibers for they do not produce permanent paralysis, though in all cases some motor weakness results. The tremor recurs if a degree of motor power impairment does not persist.

Study of such cases reveals some interesting data. For a short time after operation there is considerable motor power impairment. There may or may not be a Babinski toe sign. The Babinski may disappear in a day or two or persist. This is so also of the superficial reflexes. It seems evident that influences regulating tonus, impulses concerned with production of the Babinski toe sign, factors innervating the superficial reflexes, and those modulating the tendon reflexes travel in separate fibers in the cortico-spinal and subcortico-spinal tracts. All these activities may be abrogated in a lesion sectioning the entire pathway, but partial lesions may affect some of these and not affect others. On the other hand, we see patients who have had the dorso-lateral funiculus in the cord completely sectioned (as recommended by Putnam for treatment of tremor) in whom after a short space of time, there is little if any demonstrable residual motor weakness with return of the tremor, but with a definite persistent Babinski toe sign. In other words, pathology can occur in the pallidum and also the pyramidal tract without any alleviation of the tremor or rigidity. On the other hand, pathology

in the caudate nucleus may evidence no choreo-athetoid movements if there is also frontal lobe atrophy with implication of the cortico-spinal mechanism.

CONCLUSIONS

1. The cortico-spinal or pyramidal tract travels together with subcortico-spinal tracts through the corona radiata, internal capsule, brain stem and spinal cord.

2. All these efferent motor pathways end about the anterior horn cells and bring the collaborated influence of the higher centers on the final common motor pathway to the muscles.

3. Complete destruction of all these efferent motor pathways produces spastic paralysis, hyperreflexia, the Babinski toe sign and may abolish the superficial reflexes. The influences producing these functional alterations travel in separate fibers so that incomplete pathologic changes may result in some of these symptoms and permit other functions to continue normally.

4. For the motor cortex to function normally, the subcortical basal ganglia must be intact, and abnormal involuntary movements or altered tonus distribution resulting from pathology of the basal ganglia may not be manifest in the musculature if the motor cortex or the cortico-spinal tract is diseased.

5. Every type of motor activity is the end product of afferent stimuli, entering through the sensorium, and ultimately influencing the transmission of efferent impulses from the motor cortex through the cortico-spinal tract to the anterior horn cells in the cord.

6. Abnormal involuntary movements other than convulsive seizures do not occur if the basal ganglia are normal. It would appear that these basal ganglia nuclei arrest molecular displacements entering through the sensorium and do not permit their transmission through the cortico-spinal pathways. Disease of any of these subcortical structures permits the particular type of dyskinesia thus not adequately influenced to pass on to the cortico-spinal tract and appear in the muscles as abnormal involuntary movements.

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PSYCHIATRIC PERSPECTIVES
OF TODAY *

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MAN, in so far as he is an animal, lives only in the present. The animal has no conception of time, it has no conception of what the present is. However, the conception of time which man does possess makes possible an orientation which is singular to man, and gives it the imprint of uninterrupted life from century to century and from generation to generation. Man is inclined officially to deny his exclusive animal interest in the present, and he accumulates a past to live on, while going through the present forever aspiring to and building for a better future. The extreme form of this particular characteristic is reflected only in the monastic life of devotion. In modified forms it lives in medicine, politics, and education. We always cling to tradition and try to carry it into a future of newer traditions blended with the old.

Hence, the tradition of celebrating important anniversaries; hence also the subject of this statement. In our zealous aspiration for a better future, we are apt to project our own ardent wishes into the days to come and then present them to ourselves as predictions, even prophesies, which are to be fulfilled. What follows should in no way be construed as an attempt to prophesy, because the future can never be known unless and until it has been reached and has become the current day. What is more in order and more in harmony with scientific realism is the possible visualization of the direction lines which lead into the future, the perspectives only.

In order to attempt such a visualization, one must make an effort to rid one's self for a moment or two of the popular illusion that the world has become a small place to live in, that space and time have been conquered, and that the pace of creative thought has become so accelerated that time is no longer of real essence. This may be true

* Read before the Centenary Meeting of the Section of Neurology and Psychiatry of The New York Academy of Medicine, March 11, 1947.

only in those cases when we want to kill *en masse*, or radio-photo a new lady's hat, or popularize a new tune. It is not true, however, of the curative art, nor of any other art; these take time, contemplation, earnest and repeated calculations—these will always take time. From this viewpoint a century is a very long period—its length to be measured by the events which have occurred, by the scientific road we have travelled, by the creative life man has lived. From this viewpoint, the century the closing of which is celebrated by The New York Academy of Medicine was long, arduous, impressive, and unutterably instructive.

One hundred years ago, in 1847, Johannes Brahms was a lad of only fourteen, and today he has been dead for half a century. Westphal was Brahms' contemporary; fourteen years old the year The New York Academy of Medicine was founded, he has been dead for fifty-seven years. Baillarger died a year before Westphal; at the time of the founding of the New York Academy, he had had enough experience and aggravation with refractory, negativistic mental patients to be led to invent (in 1847) a new tube for artificial feeding. One hundred years ago, Abraham Lincoln had just started his service in the Congress of the United States; his active political life was intimately connected with the most turbulent and most bloody period in American history. Lincoln has been dead for over eighty years. In 1847 Richard Wagner was thirty-four years old, and he has been dead now for sixty-four years. Claude Bernard was Wagner's contemporary; he has been gone for sixty-nine years.

In 1847 medicine had no real conception of infectious diseases; Pasteur was barely twenty-five years old. The whole field of infectious diseases was revolutionized by Pasteur, and he has been dead for half a century now.

George Beard was an eight-year-old boy when the New York Academy was founded. He lived to become a well-established physician and a doctor of repute. He died sixty-four years ago. It was he who introduced the term "neurasthenia," which became both famous and superannuated during only half of the New York Academy's existence.

In 1847 the world had yet to wait for nearly a decade for Freud to be born, and almost fifty years before his major contributions of psychoanalysis were published. Today psychoanalysis is a household term of the amateur and the professional, the ill-concealed quack and the well-trained specialist.

Griesinger's "Pathology and Therapy of Mental Diseases" appeared two years before the New York Academy was born. It was the first truly medical, systematic textbook of psychiatry, and it was epoch-making; yet it has become nothing more than a historical datum, and today we are almost as far away from Griesinger's autopsy-psychiatry as we are from the theory of animal magnetism. And while we happen to mention this hypothesis of Mesmer, it is pertinent to recall that it was four years before The New York Academy of Medicine came into being that James Braid published his "Neurypnology, or the Rationale of Nervous Sleep Considered from the Standpoint of Animal Magnetism." It was this publication that introduced both the concept and the therapeutic implications of that which Durand de Gros christened as "Braidisme," and which has become known as hypnotism. Hypnotism enjoyed half a century of great success, had declined, had even been discarded, and then was revived very recently in combination with a revised form of psychoanalysis—all this within one hundred years.

The American Psychiatric Association preceded The New York Academy of Medicine by some three years, and the time when these two organizations were born can rightly be called the era of the birth and growth of mental hospitals. It was the era of Dorothea Lynde Dix, whose "Memorials" to the Federal and to various State legislatures sounded the tocsin of the frightful conditions in the jails, private cellars, and out-houses where the mentally ill were kept. Dorothea Dix, more than any other person, fought for the building of State hospitals. She fought in New Jersey, in Pennsylvania, in Kentucky, in Washington, in England, in Scotland. Today these very State hospitals, burdened with a great past and a very grim present, are the object of considerable criticism and attack; more than any other medical institution, they demonstrate how long one hundred years may be, how medical progress ran ahead of the State's ability and willingness to discharge its duty toward the mentally ill.

Today psychiatry seems to claim a major role in medical education, in public life, in juvenile delinquency, criminology, penology, sociological and even international and military problems. The extraordinary growth of psychiatry in positive as well as negative popularity is almost miraculous, but it is very confusing too; this growth produced two streams of medico-psychological thought which created innumerable problems in medical education as well as problems of establishing solid

scientific standards in psychiatric methodology.

One of these streams of thought could be called that of psychosociological orientation. The psychiatrist of today, if he is to acquire a modicum of clinical understanding, if he is at all to understand his patients as persons, as going-concerns called human beings, must acquire some knowledge of anthropology, sociology, and history. He must be conversant with the emotional as well as the intellectual aspects of morality, ethics, religion, and philosophy. All this was sensed many years ago; the great psychiatric reformers of the end of the eighteenth and the beginning of the nineteenth century, like Boissier de Sauvages or Philippe Pinel, were steeped in philosophy, in classical letters, and in history. Already, even one hundred years ago, the importance of anthropology was definitely felt in some quarters. It was in 1847 that the German Society of Biologists founded and held the first meeting of a special group which they called the Section of Anthropology and Psychiatry. It is noteworthy that that meeting held in Aachen was attended by Virchow, who took part in the discussion.

The psychiatrist of today does not find the needed grounding in cultural anthropology, sociology, history, and philosophy, either in his graduate or postgraduate studies. He is forced to seek out things for himself and acquire and use whatever methodology seems easier or most palatable to him. As long as this lack of medico-psychological education persists, as long as these disciplines—which for purposes of designation only could be put among social sciences—remain only a matter of the curiosity and intellectual and moral self-discipline of the given physician who happens to stray into psychiatry, as long as these uncertain and scientifically shaky conditions persist, psychiatry is bound to become a rather vague and unruly system of thought, bound to suffer from clinical unclarities, scientific inaccuracies, theoretical vagaries, and practical anarchy. The fragmentation and the schizmatic eclecticism of the many psychiatric groups and subgroups bear eloquent, even though sorry, testimony to this lack of methodological foundation and to philosophical unsteadiness. From the standpoint of the promotion of clinical knowledge and the refinement of the curative art in present-day psychiatry, the perspective cannot appear too bright even to the most inveterate optimist. For as a contemporary thinker, who wrote in defense of theory in medicine, once stated, "The technical arts and their practice always threaten the liberal arts and it is the ever present

bastard combinations of these that are called Black Arts.”*

Is not this the reputation of psychiatry in many quarters, and is not this reputation—even if fortunately undeserved—very difficult to refute before the eyes of the world of sciences? Our technological age militates against the increase of cultural and sociological education in medicine and thus does not promise much relief in the form of systematized, authoritative knowledge, except for the very, very few who are willing to risk enormous loss of time, economic security, and even civic growth. On the other hand, the ever-increasing demand on the part of the community for more and more psychiatrists makes the situation even more distressing, since efficiency alone, eclectic familiarity with terminology, and a few clinical facts cannot produce knowledge. How true this statement is may be judged from the fact that present-day psychiatry does not possess any satisfactory definition of mental illness or neurosis. A well-known psychiatrist was asked recently for a definition of a “well-adjusted person,” and he promptly answered, “A person who feels in harmony with himself and who is not in conflict with his environment.” The questioner at once asked, “Would you then consider an anti-Nazi working in the underground against Hitler a maladjusted person?”, and promptly came the reply, “I withdraw the latter part of my definition.” The questioner persisted, “How can you withdraw fifty per cent of your definition?” Moreover, we may add, our psychiatrist overlooked the fact that a goodly number of states of perfect harmony with one’s self are distinctly pathological states to be found among certain euphorias as well as stupors.

Our efficiency of indoctrination, not being able to produce knowledge, is consequently unable to produce social, scientific, and professional virtue. The famous dialogue of Plato in which Socrates proceeds to investigate the headache of Charmides can serve as a fitting summary of the situation. Toward the end of what might be called the clinical “study” by Socrates, “Charmides, without realizing the irony, . . . admitted to Socrates that Knowledge is Virtue and that he himself [was] ignorant.”**

In addition to this ignorance of substance, the psychiatrist suffers from yet another handicap which is overcome with yet greater difficulty and fraught with even greater dangers. This handicap is the

* Scott Buchanan, *The Doctrine of Signatures*. New York, Harcourt Brace, 1938, p. 5.

** *Ibid.*, p. 3.

singular essence of psychotherapy. At best, psychotherapy is a subtle art which cannot be taught; it is rather acquired by that which someone aptly called "practical contagion," by learning from one's teachers while observing them at work and not on the lecture podium.

Then, there is something even subtler than the technique of psychotherapy—it is its goal. When a patient has a laryngitis or bunion, the goal of the therapy is clear and incontestable. But let us suppose a patient has symptoms of anxiety, or character difficulties which impede his ability to work. Does restoration of his ability to work represent the true goal of psychotherapy? Let us suppose the patient's anxiety and compulsions or what-not have been removed, and let us suppose further that he still is unable to work because of some invisible and unconscious inhibitions. Is this patient to be considered cured, although he is still unable to work? Is he not apt to be considered plain lazy if he is poor, and well and fully recovered if he is rich? There is too subtle a line of distinction between idleness which is laziness and idleness which is enjoyment of permanent leisure.

The psychotherapist is thus confronted with issues of social values which creep into his psychotherapeutic goals; so do other values and prejudices creep into the business of psychotherapy, and the professional code required becomes more arduous and more complex than that of the Hippocratic tradition, which through the ages has become amplified and supplemented by our economic development and acquisitive propensities. Yet the study and teaching and learning of psychotherapy remain suspended in the air, as it were. They are left to the private judgment of anyone who takes them up, and are devoid of authority as well as tradition. The perspectives in this field are not any too bright either, although the loose and vague "moral treatment" of about one hundred years ago has been abandoned, and there are groups, such as the Freudian psychoanalytic institutions, in which at least one type of psychotherapy is considered and taught in a systematized and authoritative way. Yet the vagueness, the inarticulateness, and the confusion about the therapeutic goals are heavy shadows in the path of the Freudian, as much as they are an obscuring handicap to the non-Freudian, neo-Freudian, or psychotherapist at large.

As one casts a glance into the future and searches the psychiatric horizons, one cannot help but feel uncertain, and even puzzled; for our practical, pragmatic, highly technological age bodes ill for the

possible revival of the older tradition which demanded from the medical psychologist the qualifications of both erudition and clinical knowledge.

It is possible, of course, that a reaction may set in and that medical schools and doctors and life itself may demand the return to cultural education and to the study of man in his totality. One does not want to say that this is doubtful—but uncertain it certainly is.

In the meantime, the accumulation of borrowed theories from various fields by a multitude of contending exponents of psychological speculation do not really produce true knowledge of man, and clinical and theoretical psychopathology gives more the impression of learned ignorance than true learning, which is always humble and seldom, if ever, divisive.

I said that the end of the century which is here considered is marked by two streams of psychiatric orientation. One has just been sketched. The other was first noticed upon the medical scene under the name of "psycho-somatic medicine"—a significant and very telling phenomenon. Not new,* to be sure, but renovated by the very spirit of our practical, pragmatic age, psycho-somatic medicine established itself both as a restatement of an old error and a reassertion of a renewed unity in medicine. When some hundred years ago Jacobi and Nasse introduced the term, they not only hoped to reconcile the extremists of idealistic and materialistic psychiatries. They actually made an effort to snatch psychopathology out of the hands of the speculative philosophers and reincorporate it into medicine, to which it had belonged in the days of Hippocrates and Galen and the great doctors of the Renaissance. The dichotomy of soma and psyche was but incidental, or even accidental. In this respect, almost the same conditions prevail today as some hundred years ago.

The dichotomy of mind and body is but an artifice, and modern medicine as well as modern psychology knows it quite well, regardless of the various philosophical biases. It is quite doubtful, however, whether the average physician, considering his schooling and cultural background, appreciates that the hyphen in psycho-somatic is only a matter of spelling, that the *o* in "psycho" is merely a matter of formal, etymological construction, and that neither denotes any separation,

* Gregory Zilboorg, "Psychosomatic Medicine, a Historical Perspective," *Psychosomatic Medicine*, vol. VI (1944), No. 1, pp. 3-6; "Humanism in Medicine and Psychiatry," *Yale Journal of Biology and Medicine*, vol. XVI (1944), No. 3, pp. 217-230.

natural or artificial, of one part of man from the rest of him. This warning cannot be sounded too often or too vigorously, because medicine has been snubbing psychiatry too long, and psychiatry too long has been too timid in asserting its own scientific methodology. Consequently, there is a sort of cultural lag, a tendency to hide one's own prejudices behind hyphenated terms and still proceed along lines of old, organic formalism. The tendency to repeat old errors thus creeps upon us. The danger of this to a scientific psychiatry cannot be overestimated. As Buchanan, whom I have quoted repeatedly here, puts it, "It would be a mistake to try to add the numbers that stand for wave-lengths and hope to get a result that would still be wave-lengths; it might be still more dangerous to train [an apparatus] on a smile-illuminated face and read off the vibration rate of our sweetheart's personality . . . A great deal of the interdepartmental talk between sciences and all work in applied science run the risk of being Babelized in this fashion."*

This type of "interdepartmental talk" certainly denotes a great deal of freedom, which makes one feel free to indulge in the same type of "learned ignorance" into which the speculative psychopathologist so frequently falls. For this freedom seems to allow one to take liberties with clinical issues beyond what is permissible by empirical medicine. This methodological cul-de-sac was well described by Buchanan,** when he said that there have been times "when freedom to think has become freedom not to think, and freedom of thought has resulted in freedom from thought."

This methodological impasse imposes upon us the duty to seek a way out onto the open road which transcends the confines of the experimental laboratory proper. To leave the experimental laboratory entirely would be fatal to both medicine and psychiatry, but to limit one's self to the so many cubic feet of laboratory space, even with occasional visits to the bedside, means to leave aside and perhaps fail to learn the most important language in which man speaks. It is true that measurable data, lines, and figures are the telling language of the laboratory investigator. "But there are still other languages which he will have no admitted part in, the language of the emotions, the language of trial and error operations, the language in which he has

* Buchanan, *op. cit.*, p. 38.

** *Ibid.*, p. x.

isolated and concealed his pre-conceived ideas. It is only necessary here to point out that his success in the laboratory is based on a training and skill which are finely mixed products of the emotional arts by virtue of which he prides himself on his coolness and impartiality, of the manual arts which he has practised from childhood up, and the cultural heritage which he could not escape. These are the stuff from which the originality of genius, the laboratory atmosphere, and the international organization of science are made.”* In other words, the present-day physician must learn the language with which psychiatry is primarily concerned, and he must learn to discount certain elements of his own emotional, mostly unconscious biases, the existence of which he heretofore did not even suspect and the non-existence of which he proudly asserted in the ivory tower of laboratory research data. Still, in other words, the introduction of psycho-somatic medicine has added to the psychological and scientific burdens of medicine and surgery; it made clinical medicine and surgery even more interesting, but ever so much more complex; it relieved psychiatry of none of its duties, but it also exposed it to considerable danger, of which there are many signs on the horizon. The chief danger of them all is that of drifting into the old, outworn dualism of mind and body and that perilous path of psychophysical parallelism in which the old James-Lange, Weber-Fechner or the newer Pavlovian formulae become substitutes for the knowledge of how man functions in sorrow and in joy, in poverty and in riches, in peace and in war, in living and in dying. The temptation to reduce everything to anatomico-physiological equivalents for the psychological facts themselves, is very great indeed—just as in the days of Lavater, Gall, and Spurzheim cerebral localization threatened to take the place of understanding the human mind and produced what has become known as “cerebral mythology.”

Nor will a steady accumulation of psycho-somatic facts alone avert the danger. In the eyes of some observers of medicine, many of us have already “sunk to the level of grammars without rules, or, as the laboratory scientist would have it, facts without hypotheses”—or, we may add, even hypotheses without facts, a state of affairs which may be observed among many psychopathologists whose speculative purity divorces them from science, as well as among many psycho-somatologists whose scientific solidity does not permit them to feel quite

* *Ibid.*, pp. 29, 30.

at home with psychological factors which have no visible somatic equivalents.

Somewhat paradoxically, to be sure, we may summarize the present situation as follows:

Medicine and psychiatry have completed the circle in the course of the past century—and they have become reunited. Both accumulated during this period many more facts than were in the possession of medicine one hundred years ago. In the process psychiatry developed a sort of hyperplasia of theoretical viewpoints while medicine, burdened with palliative empiricism, began to suffer from a hypoplastic imagination and a hypertrophy of instrumental techniques. Man, as a patient and as a human, civic, and spiritual unit, gained a great deal by these developments, but as a result of the almost complete divorcement of psychiatric and medical thought, man began to lose even more than he had gained.

Whether the nearest future will bring about a proper synthesis and thus enrich the means of the curative arts and refine our understanding remains to be seen. The results unfortunately do not depend entirely upon medicine or psychiatry, or on science alone for that matter. For the severe crisis in which our whole civilization finds itself will affect us by the impact of historical forces more than we can, more than we dare to, tell ourselves.

HOSPITALIZATION OF VETERANS

A REPORT BY THE
COMMITTEE ON PUBLIC HEALTH RELATIONS
OF THE NEW YORK ACADEMY OF MEDICINE

MEDICAL care and hospitalization have become important matters of national and local concern, and there are many facets of both questions which call for thorough study and understanding. Hospital provision for the veterans, as one of the large components of the general problem, requires fundamental consideration.

The problem was looming large in 1932, when the Committee on Public Health Relations undertook a study of it and published a report. At that time there were only 4,000,000 veterans; the number has since increased to 18,733,000, and the ramifications of the problem have grown accordingly. In 1945, at the request of the Veterans Administration, we made a critical study of the veterans' hospitals for tuberculosis in New York State. The present study, even as that of 1932, deals primarily with general aspects of the entire problem.

Expanding Benefits. During and immediately following the first World War, Congress, conscious of the evils associated with the Civil War pension system, enacted laws to provide medical care for veterans who had been injured or had become ill while actually in service. The present policy of hospitalizing veterans with non-service-connected disabilities was initiated in 1924, and since that time the trend has been toward the provision of hospital care for all veterans with every kind of illness or disability, whether incurred in service or not. Admission of non-service-connected cases was at first limited to available beds and to veterans unable to pay for private hospital care. Subsequently, the interpretation of the law was apparently relaxed, and more hospitals were built in order to make beds "available" for the group with non-service-connected disabilities. Authority for hospitalization of non-service-connected cases was suspended for a short time in 1933 for reasons of economy, but it was reinstated the following year. The 1934 law added a requirement that the veteran must affirm under oath

that he is financially unable to pay for his own care, but specifically provided that his statement be "accepted as sufficient evidence of inability to defray the necessary expenses."

The Committee is reliably informed that there has been widespread abuse of this provision in connection with the application for hospitalization on the part of veterans who seek hospital care for non-service-connected disorders; comparatively affluent men are said to be signing the statement, and the Veterans Administration is by law compelled to accept these affidavits without investigation. We have been informed that the veterans' organizations have fought any attempt to apply a means test. As a result, persons who could afford private care are reported to have taken advantage of the free service, even though they must sign a statement carrying a penalty of a \$1,000 fine or a jail sentence for perjury. Indeed, the abuse in individual instances has become so flagrant that the Administration has warned veterans' organizations to police the situation, for neither Congress nor the taxpayers will tolerate it indefinitely. Dr. Howard A. Rusk, writing in the *New York Times*, February 22, 1948, stated that no case of this kind has ever been prosecuted. He cited one instance in which a veteran who died in a Veterans Administration hospital was found to have left an estate of \$250,000. In that case the government recovered the cost of the man's hospital care.

A recent extension of the conditions under which service connection may be established may create more service-connected claims for hospitalization. This is contained in a ruling by the Assistant Administrator of Claims of the Veterans Administration, issued early in 1948, which the American Legion, in its Circular No. 13, dated March 22, 1948, characterized as a "significant declaration of policy." According to this ruling, chronic disease need not be diagnosed within the one year which has been set for the establishment of service connection; a relationship may be established after that time limit if it can be shown that symptoms of a particular disease existed within the one-year period, although such symptoms may not have appeared significant when first observed. If there have been no manifestations within the one-year regulatory period, and yet a chronic condition becomes manifest later on, the case will, in the language of the ruling, "be the subject of further development in an endeavor to determine if there were symptomatology within the required period which may now be

identified or evaluated as manifestation of the chronic disease to a degree of 10 per cent or more." Thus service connection may be established for conditions that have only a presumptive relationship to war service.

One year after the enactment of the 1924 enabling act, the ratio of service-connected to non-service-connected disabilities was 5 to 1; that is, out of 6 veterans in the hospitals, 5 had service-connected disabilities and one did not. In January, 1949 the ratio was about 1 to 2; that is, out of every 3 veterans in the hospitals, 1 had a disability incident to his war service and 2 did not. There has been, therefore, a complete reversal of the situation as it existed before the 1924 amendments to the veterans' laws were adopted. The expansion of hospital facilities has seemingly been based on an intention to provide for all veterans rather than on the originally stated policy of admitting the non-service-connected cases only when beds were available. With the change in policy has come the development of a hospital empire of more than 100,000 beds, to which enormous additions have been planned; more than three quarters of a billion dollars were appropriated in 1947 for additional hospitals. Congress authorized a huge building program in spite of the fact that at various times several thousand beds have been out of service because of a shortage of the personnel needed to operate them.

Present Status of Hospital Facilities for Veterans. The 126 hospitals now operated by the Veterans Administration are constantly crowded far beyond the level generally accepted by hospital authorities as desirable for efficient service. On January 31, 1949, the number of beds actually in operation was 104,414, and the number of patients in these hospitals was 97,079, or an occupancy rate of 93 per cent. In the 33 neuropsychiatric hospitals the occupancy rate was higher, 95 per cent; in the 18 institutions for the tuberculous it was 92.9 per cent, and in the 75 general medical and surgical hospitals, 90.7 per cent. It should be emphasized that these occupancy rates are based on the number of available beds; that is, the total number of authorized beds minus the beds that are not in operation for various reasons.

According to official statistics issued as of January 31, 1949, there were 97,079 patients in veterans' hospitals and 13,474 in Army, Navy, state and community hospitals, a total of 110,553. Approximately two thirds of all these patients, 73,821, were hospitalized for conditions

that bore no relation to their military service; the corresponding figure in 1925 was about 20 per cent. The following is taken from the official statement:

Patients Hospitalized by the Veterans Administration, Jan. 31, 1949

Total	110,553
In VA Hospitals	97,079
Veterans with service-connected disabilities	31,978
Veterans with non-service-connected disabilities	65,101
In non-VA Hospitals	13,474
Veterans with service-connected disabilities	4,754
Veterans with non-service-connected disabilities	8,720

Patients with Tuberculosis and Neuropsychiatric Conditions

<i>Service-connected</i>		<i>Non-service-connected</i>	
Psychoses	22,304	Psychoses	25,875
Other neuropsychiatric conditions	1,968	Other neuropsychiatric conditions	5,283
Tuberculosis	6,726	Tuberculosis	8,380
Total	30,998	Total	39,538

Thus it may be seen that as of January 31, 1949, the number of beneficiaries with war-connected disabilities was only 36,732 (31,978 in VA hospitals and 4,754 in non-VA hospitals), for whom the facilities now available are more than sufficient.

An analysis of the service-connected cases indicates that 22,304 were suffering from psychoses, 1,968 from other neuropsychiatric conditions, and 6,726 from tuberculosis, or a total of 30,998 in these three categories. When this is subtracted from 36,732 service-connected cases, it is apparent that only 5,734 service-connected cases are in hospitals for the general run of medical and surgical conditions. That is the reason why the Chief Medical Director of the Veterans Administration holds the opinion that in order to maintain an educational and research program attractive to competent personnel, it is necessary to admit a certain number of patients with non-service-connected conditions.

The existing facilities for 110,553 patients are more than adequate to provide for all the patients whose disabilities resulted from war service, plus an additional complement of those with non-service-con-

nected disorders. But here again it should be realized that of the 73,821 veterans hospitalized for non-service-connected disabilities, 25,875 are psychotic, 5,283 have other neuropsychiatric disorders, and 8,380 have tuberculosis, a total of 39,538 in these three categories. The great majority of patients of this description are likely to be public charges, and if the Veterans Administration can provide for them, this will relieve other public authorities, state and county, from carrying the burden. We realize that in the case of tuberculosis, there is a certain hardship in the fact that patients are far away from their home communities, a situation that always leads to more numerous discharges "against medical advice." In spite of the improved service in Veterans Administration hospitals in the last few years, a recent study* indicates that except where special rehabilitation programs have been carried out,** the percentage of patients leaving against medical advice is still somewhat higher than that in the better civilian sanatoriums and hospitals for the tuberculous.

Allowing, then, for this burden of non-service-connected patients to be carried by the Veterans Administration, there remain 34,283 (73,821 less 39,538) of patients with general medical and surgical conditions not related to their military service, nearly 6 times as many as the service-connected cases in that category. If the Chief Medical Director's contention be accepted that he should have for educational purposes a number of non-service-connected patients equal to that of service-connected ones, roughly 6,000, there will still be about 28,000 who should not be hospitalized at government expense. Selection of the 6,000 who should be allowed should be made from those veterans who are economically unable to meet the cost of hospital care and those who have or have had a service-connected disability, but in addition develop ailments not traceable to their war service. If this were done, the present building program of the Veterans Administration would still far exceed the needs of the service-connected cases.

In the light of these facts, it is evident that all the expansion now in progress and any that is projected for the future will be for the care of veterans suffering from complaints in no way related to their military experience. Congress has recently authorized the construction of 89

* Tollen, W. B.: *Irregular Discharge: The Problem of Hospitalization of the Tuberculous*. Public Health Reports. 63:1441-1473 (Nov. 5) 1948.

** The Swannanoa Plan: *The Veterans Administration Rehabilitation Center for Tuberculous Patients*. Veterans Administration Pamphlet 10-26. Veterans Administration, Washington, D. C., December 1948.

new institutions, which would make available 54,000 new beds, plus additions to 11 existing hospitals. Some of these facilities will replace those in temporary buildings, which will be gradually decommissioned. It appears that if the authorized building program were completed the total number of beds would approximate 150,000. It is reported that the veterans' organizations are pressing for further construction to make available 300,000 beds in the next twenty years. If the presently authorized expansion is carried out, the ratio of beds to veterans will be 8 per thousand; with 300,00 beds there would be 20 per thousand, assuming that there will be 15,000,000 veterans alive in 1970. This ratio is in contrast to that of 4.5 beds in general hospitals per thousand of the entire population, including men, women and children.

It must, however, be stressed that the Medical Department of the Veterans Administration is not in favor of the indefinite expansion of the hospital system. The Chief Medical Director has stated that he favors an upper limit of 120,000 beds as the largest number that can be staffed and operated efficiently. The Committee considers this number as the top limit.

Since this Committee began its inquiry into the situation, the Committee on Federal Medical Services (the Voorhees Committee) of the Hoover Commission on Organization of the Executive Branch of the Government has issued its report, in which the activities of all federal hospitals are reviewed, and sweeping changes are recommended.

The Voorhees report makes the recommendation that all the medical services of the Veterans Administration, including the outpatient services in the regional offices, be consolidated with the general hospitals and certain station hospitals of the armed forces, the hospitals of the U. S. Public Health Service, and St. Elizabeth's Hospital under a National Bureau of Health. Another "task force" of the Hoover Commission, the Eberstadt Committee on National Security Organization, made a similar recommendation. Furthermore, these reports point out the huge cost of the Veterans Administration program; it ranges from \$20,000 a bed in the larger units to \$50,000 in the 100-bed units, which, incidentally, cannot be satisfactorily staffed. There are already in existence 17 hospitals so located that it is difficult to assemble staffs for them, and 12 of those being planned are also in poor locations as far as medical availability is concerned. The report comments that this situation is a disservice to veterans and a waste of tax funds.

Shortly after the Voorhees report appeared, with its analysis of the wasteful expenditure on veterans' hospitals, the Administrator of Veterans Affairs announced that on the order of President Truman plans had been made for the cancellation of 24 of the projected new hospitals and a reduction in size of 14 others, a total reduction of 16,000 beds. It was stated that the elimination of these institutions would result in a saving of \$280,000,000. The reasons given for the cancellation were: (1) the difficulty in obtaining staffs; (2) the large proportion of beds for non-service-connected patients, nearly twice as many as will be needed for the estimated maximum load of those with service-connected conditions; (3) longer serviceability than was expected of the temporary hospitals taken over from the armed forces at the end of the war; and (4) delay to afford the Veterans Administration opportunity for further study of its program.

Veterans' organizations have expressed opposition to the proposed consolidation of all federal hospital facilities and to the cutback in construction ordered by the President. The matter is presently being vigorously opposed in Congress. It is contended that the quality of medical care for veterans would be lowered and that the adjudication of veterans' claims would be adversely affected if medical and hospital services were separated from the administrative set-up of the Veterans Administration. A special subcommittee of the Senate Labor and Public Welfare Committee has recently conducted hearings on the proposed retrenchment program.

Representatives of the American Hospital Association who appeared before the Senate group were of the opinion that the President's order should be supported on the ground that the veteran himself would be the first to suffer if a mammoth hospital system were constructed without prospect of recruiting efficient staffs. They expressed no opinion as to particular hospitals that were designated for elimination from the program, but recommended, as have others, that if in the future, additional beds were needed for veterans, they should be provided through the Hospital Survey and Construction Act.

Lack of Integration in Hospital Planning. In its original report (1947)* the American Hospital Association brought out the fact that although overall planning and integration of federal hospital programs have been repeatedly recommended, the Veterans Administration "has

* "Federal Hospital Planning, with Particular Reference to Care for Veterans." American Hospital Association, 1947.

in those two categories. It is also realized that the reorganization of the medical service of the Veterans Administration since the end of the war under the able leadership of General Hawley and of his successor, Dr. Magnuson, has brought about great improvement in the administration of the veterans' hospitals and the quality of medical care rendered. Of particular importance is the establishment of affiliations with medical schools, a relationship which should be preserved, even though the eventual scope of the medical benefits to veterans be diminished.

In view of these considerations, the admission of a sufficient number of non-service-connected cases to assure a balanced research and teaching program might be justified. However, these patients should be selected from those unable to pay for their own hospital care and those of service-connected status who develop illnesses or disabilities unrelated to their war-service illness or disability.

II. The available bed complement in the Veterans Administration hospitals is more than adequate for all the reasonable hospital needs of the veterans with service-connected disabilities, and an uppermost limit should be set by Congress without further delay. We have been authoritatively informed that 120,000 is the largest number of beds that can be efficiently maintained. Both the American Hospital Association and the American Medical Association have urged that Congress place a definite ceiling to the expansion of hospitals for veterans.

III. A greater utilization of nonfederal hospitals would have reduced the necessity for the present vast extension of federal hospitals for veterans. The Commission on Hospital Care, in its report issued in 1947 following a three-year study, recommended the use of voluntary hospital facilities for governmental beneficiaries. The Voorhees report emphasizes that the expenditure in local communities of a fraction of the cost of veterans' hospital beds could furnish hospitalization for veterans near their homes. Economies could be effected by the addition of beds to existing institutions, if necessary. In Canada, where the responsibility of caring for veterans raised the same problems as in the United States, civilian hospitals have been extensively used, and in many instances, the government financed additions to community hospitals rather than build entirely new institutions for the care of veterans. There the Department of Veterans Affairs has stationed a liaison officer in each hospital where veterans are hospitalized. He

exercises no control over the running of the hospital, and the hospital authorities feel that he is there to protect both the institution and the veteran.

After the first World War the Veterans Bureau originally planned to hospitalize veterans at least partially in the existing community hospitals, and contracts were made with many institutions to provide the requisite care. But these contracts were allowed to lapse, and the great veterans' hospital building program was begun. It was costly and notoriously inefficient. At present from 12,000 to 14,000 veterans are cared for in other than veterans' hospitals, of which some are community hospitals. Those who have had opportunity to observe the arrangement report that it is advantageous both from the point of view of service rendered and from the standpoint of the remuneration received by the hospitals.

A possible hindrance to any extensive use of existing nonfederal general hospitals is the present crowded condition of most of them. A recent report by the American Hospital Association showed that occupancy is at present 82.5 per cent. It should be borne in mind, however, that the greatest utilization is in semi-private accommodations (90 per cent) and that ward beds are occupied only 60 per cent. Many hospitals find it necessary to close some part of their ward capacity. The number of ward beds out of service was said to have been as high as 36,000 in August 1947. Utilization by the Veterans Administration of available ward beds in the voluntary hospitals would not only provide ready facilities for veterans near their homes but would add much-needed income to the financially hard pressed hospitals.

IV. Another possible method of simplifying and to some extent checking the growth of the veterans' hospital system has been suggested by the American Hospital Association. This is to decentralize the system by placing control in the hands of the states and financing it by grants-in-aid. This plan would facilitate coordination with the nonfederal hospital system as it expands through the Hospital Survey and Construction Act.

As an alternative, it was suggested that if a limitation were set on the number of Veterans Administration beds, an integrated medical and hospital care program could be carried out for low-income groups, with the low-income veterans receiving federal grants-in-aid and using

local hospitals. Under that kind of arrangement it would be possible to plan hospital facilities for the population as a whole on an economical and effective basis.

V. Still another means of reducing the need for beds would be to expedite the procedures in veterans' hospitals so as to bring about shorter stays of patients. This is being done in many voluntary hospitals, where special medical committees are set up to pass judgment in individual cases on the possibilities of shorter hospitalization periods. The clinical material in veterans' hospitals is being diluted, and public funds are being wasted by the reportedly prolonged hospitalization.

VI. A stricter medical policy regarding hospital admissions might likewise result in reducing the load carried by the veterans' hospitals.

VII. Since many veterans are beneficiaries under various voluntary prepaid insurance plans covering costs of hospitalization and medical care, the Veterans Administration should advise them to make use of their contracts and seek hospitalization in the hospitals of their own communities. It has been reported that in some instances veterans who might well take advantage of the voluntary insurance plans do not do so because they expect the government to furnish such hospital and medical care as they may need. The Voorhees report suggests that the government might provide for the care of veterans with acute non-service-connected illnesses through voluntary insurance under either a private or a governmental plan.

RECOMMENDATIONS

The Committee on Public Health Relations of The New York Academy of Medicine submits herewith its report with the following recommendations for consideration by the general public, the Eighty-first Congress and the Veterans Administration.

1. As a matter of sound public policy, the Committee reiterates its recommendation of 1932 that federal responsibility for the medical and hospital care of veterans be limited exclusively to those with service-connected disabilities, except that the tuberculous and mentally ill veterans should be provided for, regardless of the origin of their disability. The comprehensive provisions in the present laws as they have been administered constitute class legislation and are detrimental to the best interests of the country. Since under existing arrangements the high quality of medical service in the veterans' hospitals can be main-

tained only if there is a variety of clinical material of interest and educational value to the medical staffs, the Committee does not object to the admission of a limited number of patients with non-service-connected general medical and surgical conditions. There would seem to be no justification, however, even for teaching purposes, for this group in any hospital to exceed 50 per cent of the total number of patients with general medical and surgical illnesses. The Committee is of the opinion that sufficient clinical material should be available through the admission of (a) patients who have been treated for service-connected disabilities and who subsequently develop non-service-connected disorders, and (b) veterans with non-service-connected illnesses who are unable to finance their own hospital and medical care. Ample clinical material for teaching purposes would be available if all the hospital services of the federal government were brought under a united administration.

2. The Committee recommends that in the group of veterans with non-service-connected illnesses admissible to veterans' hospitals should be included those with neuropsychiatric disorders and tuberculosis. Even if all veterans suffering from these two types of chronic conditions were accommodated, the existing hospitals would still afford room for a considerable number of patients with general medical and surgical conditions.

3. The Committee also recommends that Congress amend the laws to make it possible for the Veterans Administration to investigate claims by veterans with non-service-connected disabilities of their inability to pay for hospital care.

4. In view of the existing ample provision, the Committee urges that Congress place a limit to the number of hospital beds for veterans, this limit not to exceed 120,000 beds.

5. The Committee recommends that for reasons of economy the unutilized facilities of other governmental hospitals, which according to the Voorhees report to the Hoover Commission number over 46,000 beds, be made use of before provision is made for additional hospital accommodations for veterans. Large economies in personnel and costs could be effected if the federal medical services were to be integrated into a united medical administration.

6. In the interest of better planning for hospital needs throughout the country, the Committee recommends that the veterans' hospital

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BULLETIN OF THE NEW YORK
ACADEMY OF MEDICINE

CONTENTS

- Recent Advances in Our Knowledge Concerning the
Nephrotic Syndrome 605
David Seegal and Arthur R. Wertheim

- Hypersplenism 625
Charles A. Doan

- Newer Advances in Gout 651
David Adlersberg

Library Notes:

- Recent Accessions to the Library 666
-

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MAHLON ASHFORD, *Editor*

Published Monthly by THE NEW YORK ACADEMY OF MEDICINE
2 East 103 Street, New York 29, N. Y.

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE



OCTOBER 1949

RECENT ADVANCES IN OUR
KNOWLEDGE CONCERNING
THE NEPHROTIC SYNDROME*

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BRADLEY AND TYSON¹ in an excellent review last year concluded that "The nephrotic syndrome can be profitably viewed as a discrete entity. As such it remains an unsolved riddle." The purpose of the talk today is to examine the recent advances in our knowledge concerning this entity and to evaluate the various therapeutic agents which have been recommended for it.

It is unnecessary to define the nephrotic syndrome to this audience but for purposes of clarification it might be useful to review briefly its characteristics. Generalized edema, hypoalbuminemia, and heavy proteinuria are its most noteworthy features. Hypercholesterolemia and

* Presented February 18, 1949 in the Friday Afternoon Lecture Series of The New York Academy of Medicine. From the Medical Services, Maimonides Hospital, and the Department of Medicine, Long Island College of Medicine. The normal human serum albumin used in these studies was prepared by the American National Red Cross from the blood of voluntary donors. This material has been supplied to investigators by the American Red Cross as part of its National Blood Program. The opinions and conclusions are those of the authors and do not necessarily reflect the policy of the National Blood Program.

lipidemia are usually present. The absence of hypertension, nitrogen retention and severe anemia are noteworthy in most instances. The syndrome in very young children is usually described as lipoid nephrosis.² In many instances, the most careful study of these children does not allow a positive declaration as to the exact nature of the renal lesion. Apparently characteristic clinical examples of lipoid nephrosis may eventually emerge as unmistakable cases of chronic glomerulonephritis.

In most adults the persistent edema of renal origin represents a phase in the course of chronic glomerulonephritis. The remainder of these cases occur in intercapillary glomerulosclerosis (Kimmelsteil-Wilson's disease), renal amyloidosis, lupus erythematosus disseminatus, and occasionally, during the course of syphilis and renal vein thrombosis. In the past year there have been two reports^{3,4} of a self-limited nephrotic syndrome following the administration of trimethadione for epilepsy. The discussion today will be limited to facts concerning the nephrotic phase of chronic glomerulonephritis. However, under the subject of treatment, an evaluation will also be made of the effectiveness of certain agents in the control of edema of lipoid nephrosis.

Natural History of the Nephrotic Phase in Chronic Glomerulonephritis. Although the fully matured nephrotic syndrome is easily recognized, its more subtle forms are frequently undiagnosed. This has led to a considerable disparity in reports of its incidence. In a study with Bloom,⁵ it was found that evidence indicative of the nephrotic phase was present in the case histories of only 54 per cent of 50 consecutive patients dead of chronic glomerulonephritis at the Presbyterian Hospital in New York. Another 20 per cent may have had it. This left, however, 26 per cent in whom there was an absence of the criteria required for the diagnosis. Most individuals in this group were observed for periods of less than a year.

In a parallel study at the Goldwater Memorial Hospital, 10 of 11 patients with chronic glomerulonephritis observed over many years exhibited the classical findings of the nephrotic phase at some time during the course of the disease. This high incidence confirms the opinion of Baehr⁶ and that of Christian.⁷

The onset and remission of the nephrotic phase is insidious and it is particularly difficult to assign a date for the initiation of the syndrome. It is, therefore, hazardous to present precise figures as to its duration. Nevertheless, Bloom and Seegal⁵ ventured to suggest that the length

of the syndrome ranged from two months to five years. The average duration was 22.5 months.

The subclinical forms of the nephrotic state are only detected by the determination of the serum albumin and serum cholesterol values. A patient stigmatized by chronic glomerulonephritis may not be aware of the presence of slight edema; or the edema may be ascribed to a non-renal mechanism. If the serum albumin level is abnormally low it is good evidence for the presence of the nephrotic phase. Hypercholesterolemia is a confirmatory finding. Neither of these laboratory determinations should be interpreted out of context. It is presumed that the other causes of such abnormal values would be weighed. Caution should be exercised in depending upon total serum protein figures alone. It is possible that a coincident hyperglobulinemia may mask a depressed serum albumin to produce a net total serum protein value within almost normal limits.

The edema associated with severe dietary protein depletion or cardiac failure can usually be differentiated from that of the nephrotic phase. The former responds promptly to a highly nutritious regimen. The latter is evaluated in terms of the existing circulatory dynamics and the usual therapeutic aids.

When the edema is due to a combination of factors, physiological dissection is sometimes necessary to weigh the various forces. The following case report describes one aspect of this problem. The patient was a man of 36 with chronic glomerulonephritis of unknown duration. He was observed in the nephrotic state for a two year period. His serum albumin level was 3.1 gm. per cent. Edema was moderate. The patient left the hospital against advice and for the next month lived on a fluid diet consisting essentially of alcohol. He returned to the hospital in extremis with anasarca of the most flagrant type. His serum albumin value was 1.8 gm. per cent. He was immediately placed on a high protein diet and within the next month his serum albumin increased to 2.7 gm. per cent. The edema diminished coincidentally. In effect, the patient now clinically and chemically approximated his pre-bacchanalian state. Large amounts of dietary protein supplements did not further increase his serum albumin level nor decrease his edema. It is apparent, therefore, that the known edema producing factor of protein depletion has been separated from the unknown edema producing factor in the nephrotic syndrome.

The presence or the history of the occurrence of the nephrotic phase is a useful aid in the diagnosis of chronic glomerulonephritis. It serves to differentiate this disease from such other common causes of renal failure as pyelonephritis and arteriolar nephrosclerosis. In the study with Bloom⁵ it was found that among 120 patients dead of renal failure there were no classical instances of the nephrotic phase in 50 patients with arteriolar nephrosclerosis or in 20 with pyelonephritis. Although edema occurred in about one-half of the patients in these two groups it was, in most instances, related to heart failure or severe malnutrition. Loeb⁸ has stated that the nephrotic phase does not occur in arteriolar nephrosclerosis. Weiss and Parker,⁹ and Fishberg¹⁰ report the infrequency of generalized edema in pyelonephritis in the absence of heart failure. Mansfield, Mallory and Ellis¹¹ have again emphasized the absence of the nephrotic phase in a series of patients with arteriolar nephrosclerosis and pyelonephritis.

Neither the precise anatomical nor physiological changes in the kidney have been described to explain the development and the disappearance of the nephrotic phase. Nevertheless, it was of interest to determine the degree of tissue immunity induced during this state. The question of repetition of the nephrotic phase was therefore investigated. This may not be a valid question since many of the patients who emerge from the nephrotic phase enter a relatively short pre-uremic terminal stage. Irrespective of this consideration, the existence of the repetitive nephrotic phase has not been clearly established in our patient material. The few examples which have been described may very well represent fluctuations between the clinical and sub-clinical levels of the syndrome or edematous states due to more than one cause.

Some Physiological Considerations in the Nephrotic Syndrome. Starling's hypothesis¹² was stressed by Epstein¹³ to explain the edema of the nephrotic syndrome. Starling postulated that the opposing action of the capillary blood pressure on the one hand and the plasma colloid osmotic pressure on the other largely controlled the flow of fluid into and out of the capillary vessels. Extracellular fluid distribution was thereby controlled. The oncotic pressure of the interstitial fluid and tissue tension were also factors in balancing the transcapillary pressures. Low tissue pressure and high distensibility of the skin govern the localization of edema fluid in areas such as the eyelids, genitals, and the

abdominal wall. Lange and his associates¹⁴ applied a fluorescein technique to the study of capillary permeability in the nephrotic syndrome. They suggested that there was diffuse damage of the capillary membranes in this condition.

The appearance of edema in patients with the nephrotic syndrome is preceded by a long continued proteinuria attributable to a defective glomerular membrane. There is no evidence to suggest a significant excretion of protein by the tubules but reduced tubular protein reabsorption may be a factor. According to Addis¹⁵ the proteinuria in glomerulonephritis is too small to account for the depletion of plasma and body proteins if synthesis continues at its usual rate of 55 gm. per day as described by Co Tui and his associates.¹⁶ Addis hypothesizes that there is either a deficiency in this synthesis, for which there is no good evidence, or that proteins filtered through the glomerules run into a "digestive" block when absorbed through the tubules. Oliver¹⁷ has presented experimental evidence which indicates that the metabolic processes of protein absorption in the proximal convoluted tubules may be disturbed. Addis has therefore suggested that "Perhaps failure of intracellular digestion is responsible for the accumulation of protein in the proximal tubule."

Whatever the mechanism for protein loss through the kidneys, there is a reduced serum albumin level with a concomitantly reduced colloid osmotic pressure. This is generally conceded to be a prime factor in the production of edema through a disturbance in the transcapillary balance of forces. However, the occurrence of spontaneous diuresis and loss of edema in the absence of any detectable change in plasma protein concentration is difficult to explain on this basis alone. There is no reliable evidence to suggest that the formation of abnormal proteins plays a role in the formation of edema.

In addition to hypoalbuminemia, there is probably sodium, chloride and water retention due to an imbalance between glomerular filtration and tubular reabsorption. Luetscher,¹⁸ in studying the effect of intravenous salt-poor normal human serum albumin on nephrotic edema, found only a slight rise in serum protein concentration while glomerular filtration increased and the proportion of sodium reabsorbed diminished. He concluded that the reabsorption of an excessive proportion of sodium by the renal tubule is responsible for the edema of nephrosis and is of greater importance than the depressed serum albumin level.

Fox and McCune¹⁹ have stressed another phase of electrolyte imbalance which they feel might explain the diuresis which occurred in the face of a depressed, unchanged plasma protein content, as noted by Loeb and his group.²⁰ They describe instances of low plasma sodium levels and low urinary sodium excretions in patients in the nephrotic syndrome. They suggest that intracellular edema may result from this reduced plasma sodium and cause disturbed function of organs such as the kidney. They recommend the oral administration of sodium lactate and sodium and potassium acetate in doses adjusted to maintain a urinary output of 140 m.eq./L of sodium and 100 m.eq./L of potassium. It is sometimes necessary to give 30 to 50 grams of these salts daily to raise the concentrations to the optimal levels. Thereafter, a maintenance dose of 5-15 gm. of each salt is required each day. With these agents they attempt to raise the concentration of sodium in the extracellular fluid and the concentration of bicarbonate in both the extra- and intracellular fluid. Thereby, they anticipate that fluid will move out of the cells, increase plasma volume, encourage increased renal sodium excretion and thereby produce diuresis. Fox and McCune¹⁹ suggest, furthermore, that these alkaline electrolytes in tubular urine may inhibit the precipitation of protein in the renal tubules.²¹ The authors report that all fourteen patients in the nephrotic state had a diuresis on this regimen.

Robinson and Farr²² demonstrated the presence of an antidiuretic substance in the urine of three patients with nephrosis in the edematous phase and found it absent in two when they became edema free. The role of this substance in the pathogenesis of the edema must await further evaluation.

Treatment of the Nephrotic Phase. The major portion of the lifetime of the patient with chronic glomerulonephritis is symptom free. In point of fact, the presence of the disease is often only recognized by a chance urinalysis. Disability occurs during two periods: in the nephrotic state and in uremia. In the latter, the patient is usually free of edema of renal origin.

The discussion today is limited to a critique of the various suggested regimens or agents which are said to influence favorably the most distressing aspect of the nephrotic phase—edema. Before embarking on this stormy and wet journey, it might be profitable to consider with you the possibility of the effective control of glomerulonephritis. For, if nephritis could be prevented or if its earliest stages could be con-

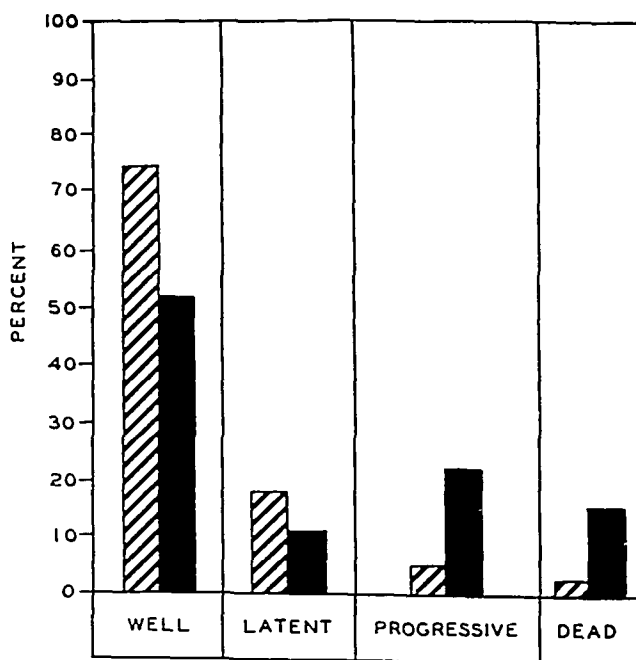
trolled favorably, in all likelihood the nephrotic phase would not develop.

The present notion is that most cases of acute glomerulonephritis follow a hemolytic streptococcus infection. A small proportion of this group progress to the chronic state. However, many patients with sub-clinical acute nephritis are not seen by a physician and members of this group, who do not heal, finally appear with chronic glomerulonephritis without a history of an acute attack. Longcope²³ believes that there are two types of glomerular nephritis: the one, the typical acute hemorrhagic Bright's disease with good prognosis and the other, a form characterized by insidious onset, persistent edema, and poor prognosis. It cannot be denied, however, that some if not all of the members of this latter group may represent the unrecognized subclinical examples of acute glomerulonephritis which have gone on to the chronic state.

Although the evidence is good to incriminate the hemolytic streptococcus as the instigator of acute glomerulonephritis, it is difficult to marshal convincing data that the maintenance of the prolonged course of chronic nephritis is dependent upon the persistence of hemolytic streptococcus infection. Exhaustive bacteriological and immunological studies²⁴ during long stages of this form of the disease have failed to yield evidence that a known biological agent was continuously active.

With the advent of the antimicrobial drugs, Williams, Longcope and Janeway²⁵ studied the effectiveness of sulfanilamide in 42 patients with acute glomerulonephritis. They gave a total of 2.4 to 3.6 gm. of the drug in six doses in each 24 hour period. The patients received a total of 6 to 169 gm. (av. 49 gm.). The sulfanilamide was administered over a period of 3 to 63 days (av. 17 days). The authors compared the course of the disease in these 42 individuals treated with sulfanilamide with that of a group of 108 similar individuals seen in the presulfanilamide days (Graph 1). They believe that the data allows them to conclude that "in the subjects receiving sulfanilamide the foci of infection have cleared up more rapidly, the signs of renal damage have disappeared more rapidly, the exacerbations of the nephritis following tonsillectomy have occurred less frequently, the duration of the edema and hypertension has been shorter, and the clinical recoveries have been greater.

"In the group of 42 patients treated with sulfanilamide there was one death in the acute stage. Complete recovery occurred in 15 of 33



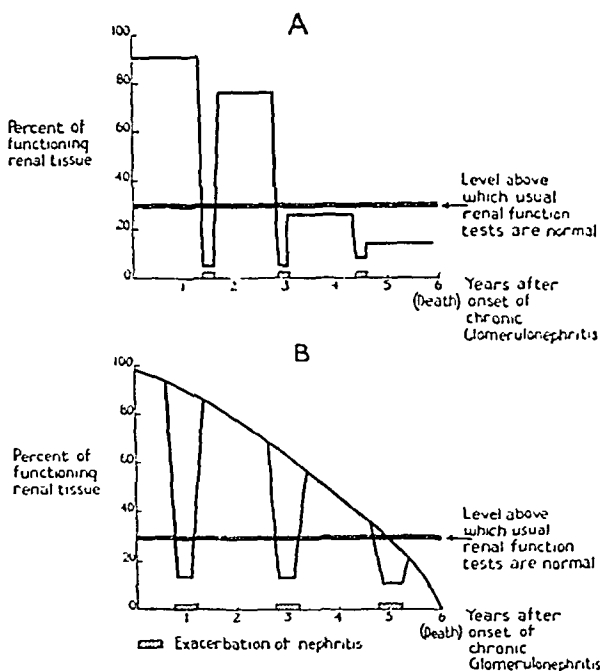
Graph 1.—Clinical outcome of patients followed for 2 years or longer. Comparison of the clinical outcome of 42 patients with acute glomerulonephritis (cross-hatch bar) treated with sulfanilamide, and 108 patients with acute glomerulonephritis (solid bar) observed in the pre-sulfonamide era. (Williams, R. H., Longcope, W. T. and Janeway, C. H. *Am. J. M. Sc.*, 1942, 203:157.)

cases who returned for observation after 6 months and in 29 of the 39 patients, or in 74.3 per cent of those followed for at least 2 years. Three additional cases who have been followed for only a few weeks are in a quiescent stage. Five of the 39 patients are in the quiescent state, and 2 are in a progressive stage.

“In the control group of 108 patients, on the other hand, there were 12 deaths in the acute stage and 5 deaths following a progression to chronic nephritis. Of the entire group of 108 patients there are only 56 complete recoveries, giving a percentage of 52; 11 patients are in the quiescent stage and 24 in the chronic progressive stage of the disease.

“The course of the immunologic reactions as exemplified by the antistreptolysin titer of the blood stream has been practically the same in both groups. There was no evidence that sulfanilamide caused renal damage in any case.”

This report has not led to general acceptance of the principle of



Graph 2—Schematic Description (*A* and *B*) Showing Two Possible Effects of Exacerbation on Mass of Functioning Renal Tissue in Hypothetical Patient with Chronic Glomerulonephritis. (Seegal, D., Lyttle, J. D., Loeb, E. N., Jost, E. L. and Davis, G. J. Clin. Investigation, 1940, 19:569.)

antimicrobial therapy throughout the course of acute glomerulonephritis. There is little doubt, however, that appropriate chemotherapy is justified in any stage of nephritis when the invading organism causes significant infection. During the nephrotic phase a variety of infections are prone to occur. These are usually amenable to the chemotherapeutic agents now available but the life-saving usefulness of these agents is not to be construed as affecting the natural history of the underlying disease.

There is inadequate evidence to relate precisely the persistence of the chronic stages of nephritis with infection. Two possible forms of pathogenesis²⁶ are schematically shown in Graph 2. In hypothetical form A, each successive infection exciting an exacerbation in a patient with chronic glomerulonephritis might produce fresh parenchymal damage and decreased renal reserve. This is the prevailing thought with regard to the pathogenesis of rheumatic fever where it is believed that repetition of the bouts of the disease produce the additive damage

leading to cardiac failure. If this same pattern exists in chronic glomerulonephritis, one might be justified in placing individuals with this disease on a suitable chemoprophylactic regimen to minimize hemolytic streptococcus infection and its effects on the kidney. However, some of our patients who have had frequent exacerbations of nephritis have experienced a rather benign course. In contrast, other patients, who appeared to be unusually free of hemolytic streptococcus infection and exacerbations over a series of years, have progressed to the uremic stage.

The observations of Masugi,²⁷ Smadel^{28,29,30} and many others have shown conclusively that the pathologic and clinical counterpart of human chronic glomerulonephritis may be produced in animals by the single injection of a specific antikidney serum. Recently Cavelti³¹ has presented evidence that autoantibodies to kidney may play a role in glomerulonephritis.

If this analogy can be carried over to man, the scheme shown in hypothetical form B may be discussed. Here the initial nephritis is followed by a progressive decrease in renal function. The course and slope of the disease may have been established at the onset. The effect of the exacerbation may be dramatic but not necessarily effective in influencing the course. The correct answer may lie in a combination of these two possibilities.

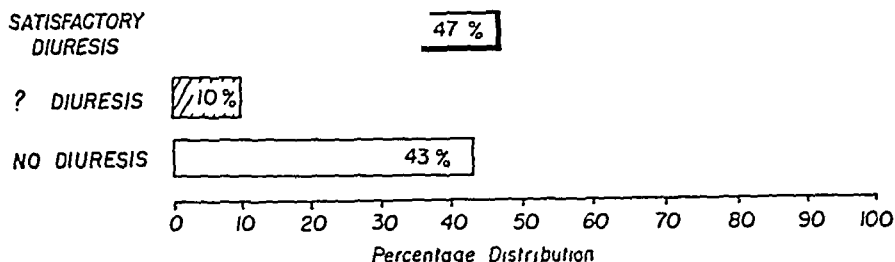
If form B represents the mechanism for progression in human glomerulonephritis, obviously prolonged chemotherapy would be unjustified. Instead, a method for blocking a specific antigen-antibody reaction would have to be developed. With respect to this point Lange and his associates³² have recently described data which lead them to conclude that glomerulonephritis is caused by a continuous organ-specific antigen-antibody reaction.

The Patient and His Edema. The most distressing symptom of the nephrotic phase is the edema. It may persist for 5 years, its average duration being in the neighborhood of 2 years. There are no means available at the moment which will guarantee that all patients in the nephrotic phase will be relieved of all their dropsy. It often becomes necessary for the patient to learn to live with some edema. Very often the patient is less concerned about his swelling than he is with the strict prohibitions presented to him concerning his diet. The methods now available to the physician to assist the patient in this state will now be considered.

EFFECTIVENESS OF SALT-POOR ALBUMIN AS A DIURETIC IN THE NEPHROTIC SYNDROME

(From Reports of Am. Nat. Red Cross)

No. of Patients 81
Courses of Albumin 103



Graph 3

Effectiveness of Salt (NaCl) Restriction in the Nephrotic Syndrome. Widal and Javel³³ in 1904 found that salt restriction in normal individuals led to a diuresis and weight loss. They furthermore noted that when these same individuals were placed on a high salt diet they gained weight, which was presumed to be fluid. A salt (NaCl) restricted diet for patients with edema is in common use today. The chief dissenting opinion is that of Fox and McCune¹⁹ who, as stated earlier, have presented data which lead them to conclude that the edema of the nephrotic syndrome is dispelled more efficiently by the ingestion of sodium lactate and potassium acetate than by a salt-poor regimen. Fox and McCune report a complete diuresis in 14 patients who underwent this treatment. Acceptance of this form of therapy must await experience with the method in other clinics.

Certain of the diets now being advocated for the alleviation of edema may owe their efficacy to their low sodium content. The usual diet for a patient with the nephrotic syndrome limits the salt intake to one to two grams per day. The Kempner³⁴ rice diet contains 0.2 gm. of sodium and 0.15 gm. of chloride. On these low salt regimens the majority of patients may learn to live a reasonably normal life with a minimal amount of edema. The exact amount of salt in their diet

able diuretic response occurred. It is difficult to ascertain from the published reports how long the non-edematous state prevailed after the diuresis. In only one-sixth of the courses is there an absence of a diuretic effect. A favorable diuresis occurred twice as frequently following the acacia regimen as when salt-poor human serum albumin was the therapeutic agent. It is difficult to compare the patient material in both series but the impression is gained that it did not differ markedly.

Lehnhoff and Binger⁴⁴ recommend the following schedule of treatment with gum acacia. The standard intravenous dose is 500 cc. of 6 per cent acacia in 0.06 per cent sodium chloride solution. This dose of 30 gm. is either given on 3 successive days or on 3 alternate days so that a total of 90 gm. is administered. The serum level of gum acacia is determined one day after the last injection. If it is found that this level is greater than 2.0 gm. per cent, no additional acacia is given. If the serum level is less than 2.0 gm. per cent and the patient continues to have edema, acacia therapy is maintained at the previous rate until either the patient is edema free or a serum level of 2.0 gm. per cent is reached. The average patient receives a total of between 90 and 180 grams of acacia for the course.

Goudsmit, Binger and Power⁴⁵ noted that the patients who received acacia showed a diminution in the serum protein level averaging 22 per cent. This drop reflected an increased circulating plasma volume. The colloidal osmotic pressure of the serum was increased in 43 per cent, unchanged in 39 per cent, and decreased in 18 per cent of the 28 patients studied. The changes in colloid osmotic pressure appeared unrelated to the degree of effectiveness of the treatment. The authors suggest that the action of acacia may be effected by a renal factor, namely chloride diuresis.

It is difficult from the data to evaluate the usefulness of the various adjuvants which have been used with acacia. However, the diuretic effect of acacia does not preclude the similar effect of another agent.

The chief objections to the use of acacia have been the reports of its long persistence in the blood stream and its deposition in the liver. Recently Mannix⁴⁶ has described death in a child of 5 with the nephrotic phase of chronic glomerulonephritis to whom more than 200 gm. of acacia had been administered. Mannix believes that the death was related to the injection of acacia.

Dick, Warweg and Andersch⁴⁷ noted a marked lowering of serum

TABLE I—COMPARATIVE DIURETIC EFFECTS IN CHRONIC RENAL EDEMA OF CHILDREN

(Based on data by Janeway et al [Tr. A. A. P. 1948])

	<i>I.V. Salt-Poor Albumin</i>	<i>Induced Measles</i>
Urine Protein	Quantitative Excretion	Decreased Excretion
Serum Protein	Slight Rise	Significant Increase
Freedom from Edema	Transient	1-6 Months
Patients Improved	50-60%	{5 of 5 with Lipoid Nephrosis {3 of 7 with Nephrotic Syndrome

proteins and a large tender liver in each of four patients who received acacia. They did not believe that this fall in proteins was a simple dilution effect. Further studies by Andersch and Gibson¹⁸ revealed that only small amounts of acacia injected into rabbits and dogs were excreted in the urine, while the livers of rabbits contained 50 per cent of the injected acacia and the livers of dogs 30 per cent. They also studied two nephrotic patients. One received a total of 72 gm. of acacia of which only 14.6 gm. were excreted in the urine. In the second patient, 43 per cent of the injected 46 gm. was found in the liver. Yuile and Knutti¹⁹ injected dogs with one weekly dose of about 2 gm. of acacia per kilogram of body weight for a period of 15 to 22 weeks. These dogs received a total dose of acacia ranging from 327 gm. to 671 gm. They exhibited a drop in plasma protein of from 42 to 71 per cent and a drop in blood fibrinogen of from 58 to 79 per cent. This reduction in fibrinogen was out of proportion to and more marked than the plasma protein fall. The authors, therefore, suggest that liver damage had occurred. Smalley, Binger, Bollman and Power²⁰ in 1945 restudied the problem of acacia toxicity. In a period of 76 days, 3 dogs received 8, 22 and 26 times the amount of acacia usually given to patients. In these dogs large amounts of acacia were found in the liver, but there was no evidence of impaired hepatic function, as measured by the bromsulfalein retention test, and the prothrombin and fibrinogen determinations. In support of this group, Johnson and Newman²¹ concluded that the reduction of blood proteins and hematocrit after acacia therapy, in 8 patients with the nephrotic syndrome, was primarily

the result of an increase in plasma volume. They found no evidence of inhibition of plasma protein formation.

The Diuretic Effect of Induced Measles on the Nephrotic State in Children. Janeway and his associates⁵² were impressed by the diuresis which occurred in a nephrotic patient who contracted measles on one of their wards. Blumberg and Cassady⁵³ were also aware of this relationship. It was common knowledge that a similar diuresis followed many infections but Janeway believed that measles was a particularly effective agent. After careful selection of patients and explanation of risks, he inoculated children in the nephrotic syndrome "by the nasal instillation of throat washings, taken in broth from patients in the Koplik spot stage of measles, treated with several hundred units of penicillin, and stored at -70° C. No attempt was made to modify the measles, but full doses of penicillin, and sometimes sulfadiazine or streptomycin were given throughout the febrile stage of measles in order to prevent secondary bacterial infection."

Twelve children were treated over a three year period. All five patients with lipoid nephrosis diuresed but only 3 of 7 patients in the nephrotic phase of glomerulonephritis lost their edema. The diuresis when it occurred appeared from the last day of fever to 8 days later and was consummated within 3 to 5 days.

Table I illustrates the comparative diuretic effects of intravenous salt-poor human serum albumin and induced measles observed in children by Janeway. The striking difference concerns the proteinuria. Under the salt-poor human serum albumin regimen, most if not all of the injected material appears in the urine. In contrast, in induced measles there is a sharp drop in the degree of proteinuria. This precedes the diuresis by 2 or 3 days. In these patients there is a significant rise in colloid osmotic pressure and total serum protein concentration. This is not generally observed in the albumin treated individual. Furthermore, the diuretic effect in the latter is transient. In the patients with induced measles, remissions have persisted for 1 to 6 months. Although none of the group are cured or healed, "the first three patients (followed for 3 years) are edema free, but still have a little proteinuria."

Since the initial effect in induced measles is a sharp drop in proteinuria, Janeway and his associates were attracted to the notion that the kidney, rather than an extra-renal site, was the area of major disturbance in lipoid nephrosis.

CONCLUSIONS

A review of the more recent knowledge concerning the nephrotic syndrome permits the following conclusions:

1. The majority of patients in a prolonged course of chronic glomerulonephritis experience the nephrotic syndrome.
2. The subclinical forms of this state are often undetected. Serum albumin and cholesterol determinations assist in establishing its presence.
3. Although the onset and remission of the nephrotic syndrome are often insidious, it would seem that its duration may extend from 2 months to 5 years with an average of 2 years.
4. The repetition of the nephrotic phase could not be established in a long series of case reports.
5. Since the nephrotic phase does not appear during the course of pyelonephritis and arteriolar nephrosclerosis, its reported or actual presence is often a useful diagnostic feature in the determination of the nature of the kidney lesion in patients presenting themselves in renal failure.
6. The mechanism to explain the formation and disappearance of edema is not well understood.
7. The dietary restriction of sodium chloride remains the most useful agent to control the edema of renal origin. However, recent studies have indicated that diuresis may occur in the nephrotic phase following the oral administration of sodium lactate, sodium acetate, and potassium acetate. This observation requires further investigation.
8. The intravenous administration of salt-poor normal human serum albumin produces a satisfactory though temporary diuresis in about one-half of the patients in the nephrotic phase. The natural history of the disease appears to be uninfluenced by this regimen.
9. A review of the case reports indicates that gum acacia is an effective diuretic agent in the nephrotic phase. At least four-fifths of the individuals so treated have experienced a diuresis. The retention of acacia in the liver is a limiting factor to its general use. Some clinicians are opposed to its use because of its long retention in the body. Recently a death has been reported in a child of 5 following the administration of acacia.
10. Induced measles produced a prolonged diuresis in all 5 patients with lipoid nephrosis. A similar diuretic effect occurred in 3 of 7

individuals in the nephrotic phase of chronic glomerulonephritis.

11. A comparison of the effectiveness of intravenous salt-poor normal human serum albumin with induced measles led Janeway and his group to conclude that whereas albumin therapy caused a quantitative appearance of albumin in the urine, induced measles produced a sharp diminution of proteinuria before the diuresis. This finding led Janeway to place the site of the defect in lipoid nephrosis within the kidney.

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HYPERSPLENISM *

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It has been the usual experience in medicine, that as scientific knowledge about disease grows, the number of etiologic entities within any given clinical syndrome increases, with a corresponding expansion and diversity of specific therapy. Tonight, we shall be discussing the much rarer opposite phenomenon, viz., a mechanism, hypersplenism, which appears to be common to a wide range of clinically and etiologically separate syndromes, for all of which, nevertheless, one therapeutic procedure, splenectomy, is now advised. It seems not to depend upon whether the symptoms are chronic or acute, whether they reflect recurrent and prolonged invalidism, or present as a rapidly fulminating emergency, which may threaten the survival of the patient in a matter of hours,—the results of splenectomy are equally dramatic.

John H. King of Johns Hopkins, reporting in August 1914 on "Studies in the Pathology of the Spleen,"¹ which he had just completed with Eppinger in Vienna, observed that "many diseases of the blood are associated with striking changes in the morphology of the spleen. Often, indeed, the gross change in this organ is the dominating feature of the clinical picture . . . yet little progress has been made in the attempt to correlate changes in the spleen with clinical symptoms. That this organ has important functions can hardly be questioned. There is, for example, considerable evidence to show that the spleen may have a marked influence on hemolysis. It is but a step then to assume that there may exist for the spleen conditions associated with an hyperactivity of some of its functions, let us say the function of influencing hemolysis. To such a condition the term "hypersplenism" may be applied . . . If it can be shown that important clinical symptoms consistently point to a hyperfunction of the spleen, and that these symptoms disappear, or are strikingly mitigated, when the spleen is removed from

* Presented at the Stated Meeting of The New York Academy of Medicine, February 3, 1949.

psychic (adrenalin) stimulation.¹⁰ The diagnostician may take advantage of this neuro-muscular mechanism to obtain a non-surgical "biopsy" of the potentially mobilizable splenic cell content at any desired moment by securing peripheral blood cell and blood volume studies before and after the injection of adrenalin.¹¹ A biphasic curve of total cell and differential fluctuations will reflect within 60 to 90 minutes the initial contraction and subsequent compensatory hyper-relaxation of the spleen before it returns to its pre-adrenalin tonal equilibrium. By preceding such a study with sodium pentobarbital, it is possible to induce an initial relaxation of the muscular tone of the spleen with an increase in its sequestration of the blood elements reflected by a transitory reduction of as many as 37 per cent of the circulating erythrocyte population.¹²

This ability of the spleen to change its volume has been known for a long time, at least since 1723, when Stukeley¹³ observed the spleen to enlarge in size as he injected blood into the jugular vein of dogs. The direct relationship, which has been repeatedly observed to exist between changes in spleen volume and circulating cell volume has inevitably focused attention sharply upon the nature and character of the circulation, which must govern this reservoir activity,—and as a direct corollary, the extent and effect of such storage on the involved blood cells. Increasingly ingenious methods have been developed for studying this most richly vascularized organ in the body. Proceeding from the older fixed tissue techniques, Knisely¹⁴ perfected the procedures for direct observation by transillumination of the living intact spleen in a number of animal species, and concluded, contrary to Mollier¹⁵ and Mall,¹⁶ et al, that the circulation everywhere within the splenic pathway is closed. Large intercommunicating sinuses, with afferent and efferent physiologic sphincters, connect arterioles and veins, permitting periodic closure when distended with blood, in which phase the plasma passes through the sinus wall by filtration, leaving the red cells concentrated and completely shut off from the active circulation for as long as 10 hours at a time. MacKenzie, Whipple and Wintersteiner,¹⁷ however, in attempting to repeat Knisely's observations on the spleen in the living animal, failed to confirm his interpretations. They believe the chief concentration of erythrocytes is in the splenic pulp rather than in the sinuses, the parenchyma receiving its complement of red cells through fenestrations in the club-like ampulae of Malpighi at

the ends of the capillaries. The red cells appeared to be slowed down or "blocked" from time to time by aggregations of white corpuscles, which subsequently gave way to permit re-entry of the erythrocytes through openings in the walls of the veins, synchronous with and mediated by the rhythmic contractions of the spleen which occurred as originally described by Barcroft.

During the spring of 1947, Sven Erik Björkman published a very complete monograph on the Splenic Circulation¹⁸ from Prof. Faraeus' laboratory at the University of Upsala. He critically analyzes the investigations of the past 100 years, adding his own experimental animal and human studies in an attempt to extend and clarify the earlier observations. Using gelatin to induce erythrocyte rouleaux formation, and saponin to produce less elastic spherocytes in rabbits, Björkman found that the pulp cords contained very few and the sinuses most of the red cells, whereas in the untreated controls there was a more equitable distribution between pulp and sinuses. He interpreted this to suggest that small changes in the size and shape of suspended particles, or aggregations of particles are important to their vascular filterability. By injecting intravenously starch granules measuring 1 to 5 *mm* in diameter, and identifying their intra-vs extra-vascular position, it was possible to further measure the approximate size of the suspected stomata under various conditions. Whereas under physiologic conditions 95 per cent of the starch granules 1 *mm* or less in diameter were found to have passed into the pulp cords, while 80 per cent of the granules 5 *mm* were still in the sinuses, after inducing an acute splenic tumor by experimental streptococcus infection or by intoxication with an hemolytic agent, only 50 per cent of the larger starch granules remained within the sinuses. An enlargement of the vascular stomata, under these pathologic circumstances, was hypothesized. Transferring his observations to selected human autopsy material, Björkman believes he has evidence to support the concept of an identical human splenic vascular mechanism, in which in acute splenic tumor in man there is sinus dilatation with an accelerated intercourse for both plasma and corpuscular elements between sinuses and pulp cords, via broadened and distended stomata. Conversely, in chronic cardiac decompensation and hepatic cirrhosis, Björkman describes a pathological modification of the splenic sinus wall structure, as reported earlier by Matsui,¹⁹ with an increasing number of longitudinal anastomoses between the normally

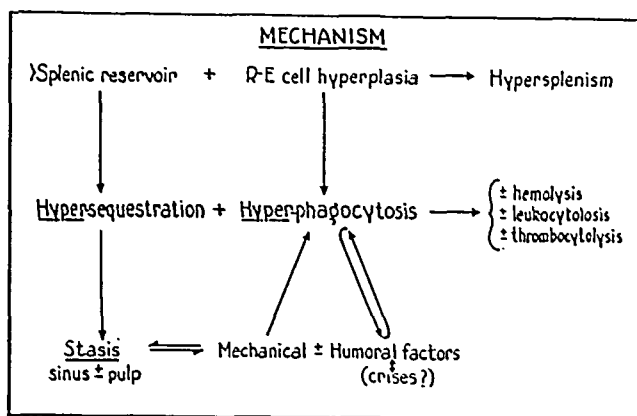


Figure 2—Mechanism of hypersplenic states, theoretical considerations.

annular fibrils in the sinus and venous walls, which would tend toward a compensatory preservation of the tightness of the sinus filter in resistance to a mounting portal hypertension.

Watzka²⁰ and Snook²¹ have separated the various species in which the splenic circulation has been studied into two major groups: 1) those with poor sinus development, viz., cat, dog, cow, horse, sheep, swine, hedgehog, mole, ermine, weasel, and mice, and 2) those rich in these vascular structures: man, ape, rabbit, guinea pig, rat and squirrel. This variability in species and in pathologic splenic state may well explain the variations in emphasis in the study of an organ where it now seems certain that both sinuses and pulp cords are important circulatory reciprocals.

Thus it would seem fair to accept as our current working hypothesis (Fig. 2) the concept that the human spleen has a semi-open circulation, controlled by a filter mesh mechanism in the sinus wall, which by heredity or under many diverse pathologic conditions may be altered, either in the direction of greater or lesser selective permeability to the cellular elements of the blood. This circulatory mechanism, unique as compared with all other organs and tissues, operates to separate the cells from the plasma, and thus to concentrate in the spleen, both within and without the sinuses, in varying degree and quantity, blood cells of various types and quality.²² The more disturbed the circulatory equilibrium, the more profound and prolonged the stasis, the more does the

spleen seem to lack discrimination and to withhold normal as well as fragile, senile and damaged elements.

The hypersplenic sequence of events may well include: abnormal stasis within splenic sinuses and/or pulp^{23,24} calling for a compensatory increase in delivery of marrow elements; deplasmazation with increased mechanical intercellular friction;²⁵ loss of erythrocyte potassium with other electrolyte disequilibria, leading to increased fragility;²⁶ pathologic concentration of lysolecithin and lysolecithin-like, spherocyte-inducing biochemicals normally produced in physiological amounts by the R-E cells,²⁷ with hemolytic blocking^{28,29} or other polyhemagglutinin antibodies³⁰ theoretically derivable from the R-E cells, exceptional opportunity for immediate contact-phagocytosis by R-E elements;—all in all an ideal environment for the establishment of a vicious cycle of cell withholding and cell destruction capable of acceleration or deceleration, depending upon a variety of factors. The dramatic immediacy of the termination of a true hemoclastic crisis at the operating table, at the moment of ligation of the splenic pedicle, strongly incriminates this inherent, chemico-mechanical splenic mechanism.²

THE ROLE OF THE BONE MARROW

Turning now from the spleen *per se*, what role, if any, does the bone marrow play in the human hypersplenic states? The microcytic, spherocytic, hyper-fragility of the erythrocytes associated with the hemolytic syndromes has been attributed to an inherited, inherent marrow defect.³¹ Dameshek³² and others have proved that all of these qualities are readily acquired by the definitive erythrocyte after marrow delivery, and it is difficult, if not impossible, to demonstrate these characteristics in the reticulocytes obtained directly from the marrow in these patients. The reports^{33,34} of a normal survival time for transfused erythrocytes from normal donors in patients with acute hemolytic crises, in contradistinction to a relatively shorter survival time for their own marrow product,—and that such transfusion support should be given routinely,—have not been confirmed in our experience. On the contrary, we believe the administration of borrowed red cells in acute hemolytic crises is both unnecessary (Fig. 3) and extremely dangerous. Attributing the excessive hemolysis of freshly transfused red blood cells in these patients to inaccurate isoagglutinin or Rh typing, though this danger is always a possibility, can hardly account we believe, for

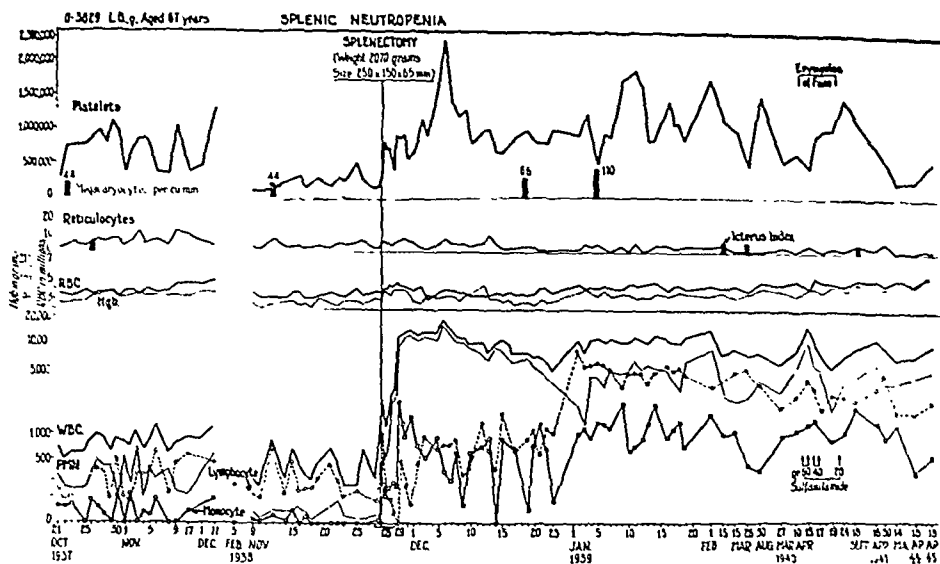


Figure 4—Primary splenic neutropenia progressing over a 12-month period to panhematopenia due to an extension of the same hypersplenic mechanism. Splenectomy completely and permanently restored the cellular and clinical equilibrium (11 years).

marrow is hyperplastic for neutrophilic myelocytes obviously maturing normally with delivery of motile band forms into the circulation at an accelerated rate; the sinuses and parenchyma in the greatly enlarged spleen have their usual complement of sequestered mature erythrocytes almost entirely replaced by these same granulocytes which may be found both without and specifically within the highly phagocytic R-E cells; the capillary circulation meantime may show as few as 25 granulocytes per cu. mm.; adrenalin contraction of the spleen may be expected to raise this circulating increment of granulocytes transitorially to 10,000 or more per cu. mm., in which case, splenectomy is almost certain to permanently correct the dyscrasia.

It will be clear from the foregoing discussion, that the bone marrow mechanism, which we have thought to be most frequently invoked in those pathologic states included in our definition of "hypersplenicism," comprises the following interrelationships: maximum compensatory hyperplasia, with normal maturation and accelerated delivery of the specific marrow element or elements involved, which elements, nevertheless, remain in dangerously low negative balance in the circulating blood, due to an increasingly complete and absolute withdrawal of

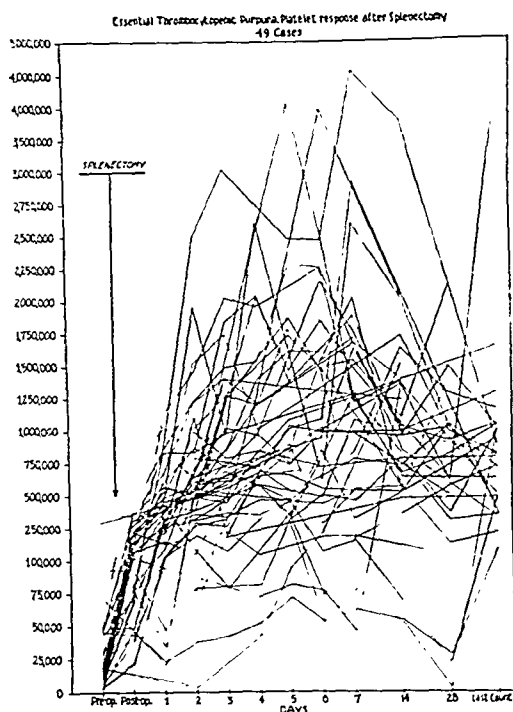


Figure 5—The peripheral thrombocyte response to splenectomy in 49 consecutive cases of thrombocytopenic purpura.

these essential blood cells by the spleen.

Final proof of the hyper-sequestration versus the marrow inhibitory role of the spleen in any given instance would seem to rest on the results of a carefully controlled study of the blood entering and leaving the spleen before and after adrenalin, during surgical exploration in an active phase of such cellular disequilibrium. During the past year we have been making such observations in appropriately selected patients with the surgical coöperation of Dr. Robert Zollinger. These data will be presented in detail elsewhere. Suffice it to say, here, that this direct evidence effectively eliminates any bone marrow inadequacy of cell maturation and delivery as major factors, at least in those patients so studied, at the same time placing the full pathologic responsibility on the splenic tissue in situ.

Reference to Fig. 5 on which are graphed 49 consecutive cases of primary splenic thrombocytopenic purpura, will reveal the immediacy,

the uniformity and the magnitude of the increase in circulating platelets which occurred at the operating table on the day of surgery, in all but five patients. Splenic artery and vein studies in a representative sampling of this series confirmed the bone marrow and adrenalin test interpretations of active platelet delivery, the splenic artery in one patient, for example, carrying 450,000 platelets per cu. mm. to the spleen, while the vein leaving the spleen contained only 17,000 platelets per cu. mm. Five minutes after adrenalin injection into the splenic artery, the splenic vein contained more than 400,000 platelets. This could be interpreted either as a closing of the sinus-pulp reservoirs temporarily by the contraction of the spleen creating an arterio-venous shunt, or it could represent a reservoir release of temporarily trapped platelets; in either interpretation the integrity and activity of the bone marrow is attested. In the five cases which showed a much slower and more gradual post-operative increase in the circulating platelets, the evidence might be interpreted as a gradual recovery of inhibited megakaryocytes reciprocal to the gradual elimination of some humoral agent produced by the spleen. Lacking as yet objective reproducible evidence of a circulating "thrombocytopen," this explanation must be left "sub judice" for the present.

In primary uncomplicated hypersplenism, then, as we have seen and interpreted these syndromes in our Clinic, the bone marrow plays only a reciprocal physiologic role, compensating, eventually maximally, in response to an excessive peripheral demand for blood cells, which demand fluctuates from time to time with the unpredictability of an inherently unstable and pathologically hyper-reactive spleen. The net increment of blood cells at any one moment in the circulating blood is always the resultant of the balance between supply and demand. Whenever any disturbance in this cellular equilibrium, so essential to health, occurs, either the supply must be increased or the demand reduced, promptly. In the hypersplenic states we must eliminate an excessive pathologic demand, more or less wholly created by the spleen, and which may or may not be compensable by the marrow. If and when the marrow becomes inadequate, the spleen must be promptly sacrificed, or the survival of the individual will be gravely threatened. Once freed of all splenic tissue, we have never found such individuals to show any further inadequacy or incompetence of the marrow for any and all demands through many years.

PRIMARY HYPERSPLENISM

Primary hypersplenism we define as an hyper-instability of the spleen, sometimes inherited as a Mendelian dominant gene factor, as in congenital hemolytic icterus, and, at other times, when direct human inheritance is difficult to establish, perhaps as a recessive character of infrequent expressivity. In such circumstances "spontaneous" hypersplenic episodes may occur, unrelated to any demonstrable internal or external environmental cause, such physiologic stresses as a normal pregnancy, and minor infections and traumata, frequently and repeatedly precipitate more or less severe hypersplenic exacerbations or "crises" in "susceptible" patients. For these reasons, whenever a true hypersplenism is recognized, prophylactic splenectomy must be seriously considered. Elective splenectomy is much to be preferred to emergency splenectomy for obvious reasons. Irrespective, however, of the degree of cytopenia or of the acuteness of the clinical syndrome, the response to splenectomy is equally prompt and sustained."

Furthermore, it is seldom that we encounter a "pure" hemolytic or an unadulterated thrombocytopenic or neutropenic syndrome. The predominant clinical picture may be anemia, with or without jaundice, or purpura, or Ludwig's angina and infection, but any one of these symptom complexes will be found more often than not to have a sub-clinical if not clinical cytopenia involving one or more of the other elements of marrow origin. At different stages in the clinical course of the same patient, differing degrees of pan-hematocytopenia may be observed (Fig. 4) reflecting the variable withholding idiosyncrasy of the pathologic spleen for the cells coming to it.

One of our patients, a 14 year old girl when first seen in consultation, had a history of more or less continuous, severe pan-hematocytopenia since birth. Every laboratory examination showed every organic function to be normal, except for a pan-marrow hyperplasia of normally maturing cells in normal relative proportions, and for the adrenalin test which was interpreted as reflecting an unequivocal splenic pan-cellular hypersequestration. Splenectomy was followed by a prompt peripheral hematologic re-equilibration, and by a complete clinical metamorphosis from chronic invalidism to normal health and physical activity. The surgery was consummated in October 1943. No other pathology has developed in the intervening 5½ years (Fig. 6).

TABLE I—SECONDARY HYPERSPLENISM

Secondary or Acquired Hypersplenism—normal instability + { unusual pathologic stress	
<i>Non specific</i> —miscellaneous constitutional diseases.	
1. Congestive	
2. Infiltrative	
3. Hemoblastic (the leukemias)	
4. Inflammatory	
5. Neoplastic	
6. Myelofibrosis with splenomegaly, with or without hematopoiesis	

TABLE II—326 SPLENECTOMIES

1932 - 1949

HYPERSPLENISM TOTAL	(82%) 270	
Primary	(65%)	176
Secondary	(35%)	94
MISCELLANEOUS TOTAL	(9.5%) 30	
Hypoplastic Anemia (relative splenic factor)		14
Polycythemia Rubra Vera		2
Sickle Cell Anemia		2
Lymphatic Leukemia		9
Myelogenous Leukemia		3
Erythroblastic Leukemia		1
NORMAL SPLEEN CONTROLS	(8.5%) 26	
Traumatic rupture (All Columbus Hospitals)		22
Secondary to other surgery (exposure)		4
TOTAL		326

there develops a syndrome identical with one or other of those already described as primary hypersplenism, in which both specific splenic hypersequestration and compensatory bone marrow hyperplasia may be demonstrated, though there is no familial history of such a trait. Hemoclastic crises may occur which threaten the survival of the individual quite independently of his basic disease. Under such circumstances splenectomy is indicated and may, and sometimes must, be undertaken,

TABLE III—270 HYPERSPLENIC CASES

1932 - 1949	
270 SPLENECTOMIES FOR HYPERSPLENISM	
PRIMARY	
Congenital Hemolytic Icterus.....	75
Thrombocytopenic Purpura	77
Splenic Neutropenia	13
Splenic Pan Hematopenia.....	11
Recurrences	
a. Accessory Spleens	4
b. Generalized R.E. Cell Hyperphagocytosis	5
SECONDARY	
a. <i>Congestive Splenomegaly</i>	
Banti's Syndrome	42
Felty's Syndrome	6
Acquired Hemolytic Icterus.....	16
b. <i>Infiltrative Splenomegaly</i>	
Gaucher's Disease	4
Xanthomatosis	1
c. <i>Hemoblastic Splenomegaly</i>	
Lymphatic Leukemia	4
Myelogenous Leukemia	2
Monocytic Leukemia	1
d. <i>Inflammatory Splenomegalies</i>	
Tuberculosis	3
Syphilis	1
Moniliasis	1
Boeck's Sarcoid	2
Hodgkin's Syndrome	5
e. <i>Neoplastic Splenomegaly</i>	
Retothelio Sarcoma	1
Hemangioma	2
Multiple Myeloma	1
f. <i>Myelofibrosis</i> with fibrous splenomegaly without myeloid metaplasia	2
(With myeloid metaplasia 4 cases, no splenectomy)	

with the more remote prognosis, however, correspondingly guarded. In no instance have we noted any exacerbation of the underlying disease process because of the splenic surgery, and most often the improvement which follows the re-establishment of a more nearly normal blood cell equilibrium is directly beneficial in the further management of the original disease.

In our series of 326 splenectomies (Table II), 82 per cent were diagnosed as hypersplenism, and of the 270 splenectomies for hypersplenism, 65 per cent have been classified as without otherwise demonstrable disease, therefore as primary, and 35 per cent as secondary to some other obvious basic pathology. Because of the frequency with which the spleen, when involved in other pathologic processes (Table III), has been observed to assume an aggressive activity against the blood cells entering its sinuses, it now seems appropriate to consider this

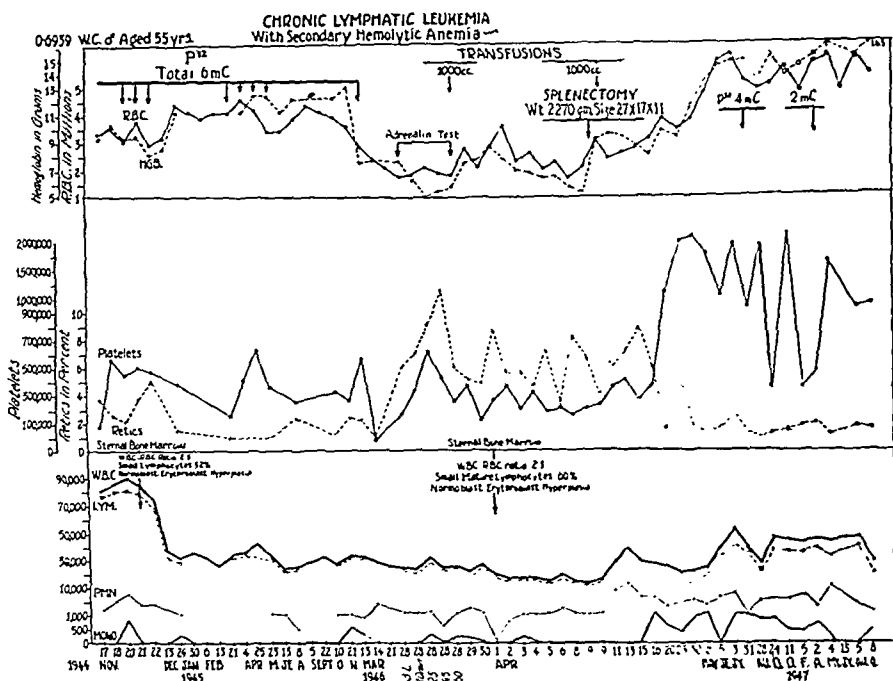


Figure 8—Acute erythroclastic crisis during the course of chronic lymphatic leukemia.

organ as possessing a considerable degree of "normal instability," not unlike, qualitatively, the inherited "abnormal hyperinstability" of the primary syndromes. The unique structure of this organ, as required for its physiologic functions (Fig. 1), lends itself admirably to circulatory disturbances associated with parenchymal cellular invasion, and the large complement of phagocytic cells already there await only the time and opportunity, which stasis and engorgement inevitably provide.

Three examples only will be cited from this series. During the course of chronic lymphatic leukemia (Fig. 8) in a white male, aged 57, who had been under satisfactory control with radioactive phosphorus for several years, there developed an acute hemolytic crisis. Appropriate laboratory studies ruled out both radiation damage and lymphocytic myelophthasia of the marrow as contributing factors while revealing a marked compensatory normoblastic hyperplasia, and splenic hypererythro-sequestration. Splenectomy was advised, after transfusions had proven ineffective, and was followed by an immediate cessation of

erythrocyte destruction. The underlying leukemia has continued to respond to small infrequent doses of radioactive P-32 to the present time. There have been no further hemolytic episodes.

A white male patient aged 39 years presented with all of the clinical and hematologic findings characteristic of acute primary thrombocytopenic purpura, including typical compensatory megakaryocytosis in the bone marrow without other demonstrable pathology. Splenectomy was followed by an immediate and sustained thrombocytosis, and the prompt disappearance of all purpuric manifestations. Histologic study of the spleen, however, revealed a well developed Hodgkin's granuloma, though neither liver nor lymph nodes, grossly or microscopically, showed any sign of this disease at this time. One year later the primary disease proved terminal, despite intensive therapy, but there was no recurrence of the purpura which had threatened survival from hemorrhage a year earlier.

A young woman, aged 20 years whose sister eight years previously had undergone splenectomy for Gaucher's disease, suddenly developed a rapidly enlarging abdominal tumor associated with profound peripheral blood changes. The total circulating leukocytes were only 1300 per cu. mm., the red cells 3,180,000, and the platelets 111,440. An adrenalin test decreased the tumor size and increased temporarily the circulating level of all of the normal blood elements. A sternal marrow study showed compensatory pan-marrow hyperplasia of all essential elements. An occasional Gaucher cell was found which served to establish the diagnosis. Similar studies of the sister's marrow revealed Gaucher cells in limited number, insufficient, however, to have influenced adversely the normal circulating blood cell equilibrium during the years since her earlier splenectomy. A 5000 gram spleen was removed without complications, followed immediately by the re-establishment of a normal sustained circulating level of all blood cells. Marriage and a normal pregnancy have been accomplished without untoward incident meantime.

Reference to Table III will show the range of diseases thus far encountered in our clinic, which have shown at some time during their clinical course, an involvement of the spleen sufficient to precipitate a more or less acute hypersplenic crisis, for which complication, surgery has been deemed imperative for survival. In none of these individuals have we been able by history or direct examination of blood relatives

to establish an hereditary factor. It is for this reason that we are hypothesizing a so-called "normal instability" of the spleen in its reservoir function for any or all of the blood cells, which due to the unique circulatory mechanism of this organ, plus its high content of R-E cell phagocytes, permits of ready imbalance in the circulating levels of the blood elements, which normally pass through or remain only temporarily in its parenchyma.

ACUTE HEMOCLASTIC CRISES

As already stated, the hypersplenic mechanism, whether primary or secondary, may precipitate some of the most acute critical acellular clinical syndromes which the physician and surgeon are called upon to diagnose and treat. Uncontrollable hemorrhage, a profound hemolytic anemia, or sudden sepsis may dominate the clinical picture. An immediate and thoroughly critical blood and bone marrow study is the first essential in the differential diagnosis. There may be insufficient time for a confirmatory adrenalin test or other extensive laboratory investigations. The theoretical considerations, which may explain this sudden negative balance between bone marrow supply and peripheral demand for any or all of the essential blood elements, we believe involve both the mechanical and/or humoral factors inherent in the vascular and cellular organization of the spleen (See Figs. 1 and 2). Whether the blood platelets, the erythrocytes, the granulocytes, or any possible combination of these elements are found to be deficient in the blood stream, the marrow must be hyperplastic for their precursors, without evidence of maturation arrest or qualitative abnormalities, if and when a true uncomplicated hypersplenism is the sole cause. In such syndromes, splenectomy is followed by a prompt and complete cellular re-equilibration, as reflected in the seven patients with acute erythroclastic crises in congenital hemolytic icterus and in the one patient with acute thrombocytopenic purpura (Fig 3). The curve of recovery of the red blood cells in each of these eight cases follows the same general pattern and timing, though the anemia in the first seven was hemolytic in origin and in the eighth it was secondary to hemorrhage. All of the factors which govern the specificity and degree of cellular deficit from patient to patient, and in the same patient from time to time are still unrevealed, but the evidence to date tends to incriminate the spleen rather than the bone marrow.

RELATIVE HYPERSPLENISM

In certain patients, who have experienced permanent marrow damage from industrial toxins, but in whom progressive mesenchymal destruction has been halted by removal from the environment, the normal physiologic reservoir function of the spleen may be sufficient to prevent cellular recompensation. After a sufficient period of supportive therapy, if the marrow hyperplasia continues to prove inadequate for the demand, splenectomy should be considered and will permit at times in selected patients, a more nearly normal circulating increment of cells.

TRAUMATIC RUPTURE OF THE SPLEEN

Control studies have been made in those healthy individuals who have suffered sudden traumatic rupture of the spleen requiring emergency splenectomy for intra-abdominal hemorrhage and shock. In a survey of some 22 such individuals, the hematologic equilibria and the health and clinical resistance to ordinary infections have remained unimpaired (Table II). The normal human spleen is apparently not essential to life or health. Conversely the pathologic human spleen may threaten both health and longevity.

POST-SPLENECTOMY FAILURES AND RECURRENCES

The importance of differential diagnosis in the establishment of a true hypersplenic syndrome cannot be overemphasized. Obviously other mechanisms may simulate superficially these specific splenic entities, the most common of which involve the bone marrow, upon the integrity of which the body is dependent for its continuing resupply of new cells throughout life. Progressive marrow hypoplasia on the basis of any nutritional deficiency or toxic etiology, intrinsic or extrinsic in origin, must be recognized and corrected per se at the earliest possible moment. Myelofibrosis and osteopetrosis may be accompanied by compensating extramedullary hematopoietic splenomegaly, which when associated with a precipitated hypersplenic episode may strongly suggest splenectomy. Under such circumstances a positive adrenalin test will usually reflect a sharp increase in circulating nucleated red blood cells and myelocytes, but on occasion such evidence of local splenic hematopoiesis is lacking. If repeated bone marrow aspirations fail to reveal active blood cell regeneration from any and

all sites (sternum, spinous process, iliac crest, ribs), it may be necessary to aspirate the splenic parenchyma directly, or secure a tissue biopsy, before a judgment may be reached as to the relative importance of the productive versus the destructive roles of the spleen in any particular instance. In six such patients only two showed a predominant hyperdestructive activity by the enlarged spleen with negligible hematopoietic function. Both of these patients benefited by splenectomy. A tightly packed avascular leukemic marrow may simulate at times, an hypoplastic state, and with a sub-leukemic peripheral absolute leukopenia, anemia and thrombocytopenia, may lead to an erroneous interpretation of the splenomegaly.

In only a very few instances, fortunately, have we encountered a generalized R-E cell hyperplasia and hyperphagocytosis, in our non-bone marrow cytopenic states, so that liver, lymph nodes, marrow and connective tissues participated sufficiently to render clinically ineffective the removal of the excessively large increment of phagocytes in the spleen. Until proven otherwise, therefore, the principal pathologic focus in these patients may be assumed to be the spleen.

ACCESSORY SPLEENS

An initial characteristic post-splenectomy remission may at times be followed after a few months or even after several years by a recurrence of the same or an entirely different type of hypersplenic syndrome. Experience has taught us to be immediately suspicious of some remaining accessory splenic tissue when this occurs. The marrow is again studied immediately and must show specific hyperplasia of the deficient circulating elements without maturation arrest or abnormal qualitative alterations. Accessory spleens or implanted splenotic fragments from a traumatically ruptured or surgically torn spleen may become hypertrophied and functionally pathologic. Re-exploration is definitely indicated when the laboratory data confirm a recurrent mechanism of hypersequestration and destruction. Thorotrast visualization will frequently assist the surgeon in locating the embryonic splenic rests in remote areas, including the retroperitoneal gutter.

Our first patient to be subjected to splenectomy during an acute erythroblastic crisis in congenital hemolytic jaundice experienced a dramatic recovery hematologically and clinically, which lasted 4½ years (Fig. 9). At the end of this period the same type of hemolytic,

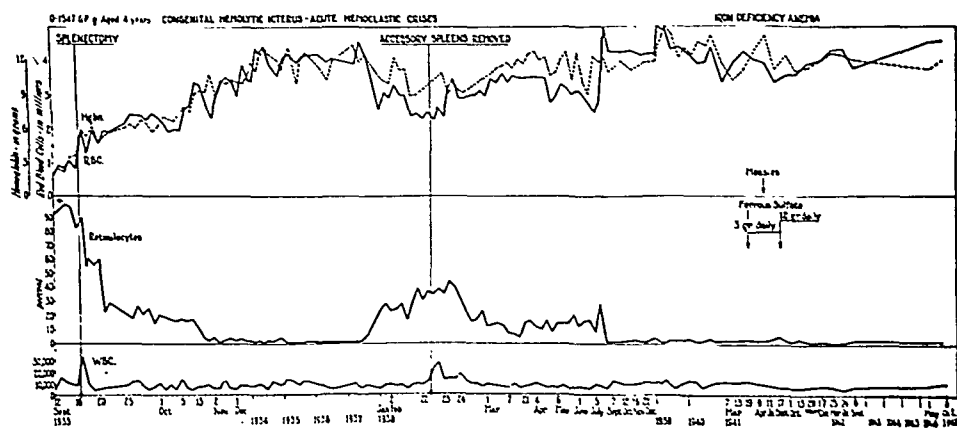
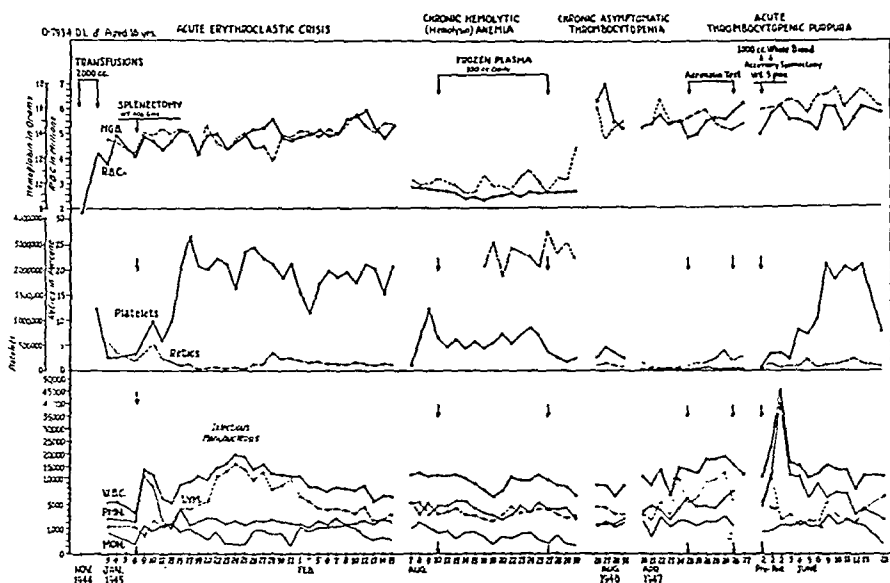


Figure 9—Recurrent hemolytic icterus caused by accessory splenic tissue. Recovery followed removal of 3 small accessory spleens.

icteric anemia re-appeared with reticulocytosis and compensatory normoblastic marrow hyperplasia identical with the first episode. When all medical measures had failed, a surgical re-exploration was undertaken and three small accessory spleens, totaling not over 5 gms. by weight in all, were found and removed. Mesenteric nodes and a biopsy of the liver were obtained at the same time from normal appearing tissues, and histologic examination confirmed the normalcy of these organs. The accessory splenic tissues, however, contained excessive numbers of highly phagocytic clasmatoocytes loaded with red blood cells, and a second remission followed their removal. This has continued to the present time 11 years later,—16 years after the first operation.

The fact that few carefully studied hypersplenic episodes represent a pure single cell strain sequestration has been previously emphasized, together with the observation that the same individual patient may at different times show different cell-type deficits, reflected by entirely different clinical syndromes—all of which tends to center attention upon splenic tissue, its unique circulatory system, functionally designed for storing normal cells and salvaging damaged and senile blood elements,—rather than upon the organ of their origin, the bone marrow. This double danger of differential splenic selectivity was demonstrated in one of our patients in two dramatic episodes separated in time by 18 months. A young man 16 years of age (Fig.10) developed without previous warning, an acute erythroclastic crisis, typical of congenital



Reference is made in this general connection to the patient already cited, who first presented with a relatively pure primary splenic neutropenia, only to develop within twelve months a splenic panhemato-

penia involving all of the circulating blood elements, with complete and permanent pan-cellular re-equilibration following splenectomy, continuing to date 11 years (Fig. 4).

Failure of complete and permanent restoration of health following splenectomy in true hypersplenic states will only be encountered in those individuals in whom the hypersplenism is secondary to progressive constitutional disease involving other organs. The ultimate outcome in such patients obviously will depend upon the effectiveness of the therapy for the primary disease. Nevertheless, when the predominant clinical syndrome in such patients can be proven to reflect an hypersplenic mechanism, this complication may and must be considered on its own merits. The best clinical judgment in our clinic has been more frequently than not to eliminate the focus of disease in the spleen together with the accompanying and resultant hypersplenic cellular imbalance, both of which threaten the health and survival of the patient. Only if a substantial cellular contribution is actually being made by a compensating, ectopic hematopoietic focus in the spleen, will the patient be less well off without rather than with his spleen.

CONTRAINDICATIONS TO SPLENECTOMY

The contraindications to splenectomy may be sharply defined and clearly stated: 1) any acute or chronic bone marrow damage; 2) myelofibrosis, and 3) osteopetrosis in which the splenomegaly usually reflects ectopic hematopoiesis; 4) pan-myelophthasia; 5) ectopic splenic hematopoiesis plus secondary hypersplenism.

SUMMARY AND CONCLUSIONS

The spleen has inherited a unique anatomical structure, in which the relationship between smooth muscle capsule, pulp, and large fenestrated sinuses makes for an ideal physiologic reservoir for blood cell storage. The selective concentration of the stored elements of the blood, through the mechanism of deplasmalized stasis,—which in turn probably hastens unfavorable qualitative alterations in these cells,—when combined with an abundance of naturally occurring R-E cells, provide a basis for an apparent inherent homeostatic cellular instability in acquired, and an inherited hyper-instability in primary hypersplenism. A sub-acute, low-grade cellular disequilibrium may lead in one patient to chronic invalidism; in another, the same mechanism may result in a

vicious cycle, in which an acutely developing negative cellular balance will threaten survival. The resulting anemia, leukopenia or thrombocytopenia, which may be highly selective and specific, or in any combination and degree, underlie and govern the wide range of symptoms and signs which characterize these syndromes. Therefore, when the bone marrow is eliminated as a contributing factor, and a basic splenic mechanism is established, prompt removal of the spleen and all accessory splenic tissue provides the only assurance of a complete and lasting hematologic and clinical remission.

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NEWER ADVANCES IN GOUT*

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GOUT is an extensively studied, and yet obscure disease. It is of great interest to many branches of medicine: metabolism, arthritis, cardiovascular and renal disease, allergy, and orthopedics. The name of the disease is unusual in medical terminology. The term "gout" is derived from the Latin gutta, a drop. It was introduced in the thirteenth century to indicate that a noxa affected a joint by falling into it drop by drop. All students of the disease are fully aware that the term is somewhat naive, antiquated and has no nosological significance. Still, it is being commonly used because of its archaic-aristocratic dignity and because it is preferable to other terms, e.g., podagra, which only connotes "pain in the foot" and therefore should be reserved for and limited to this classic manifestation of gout. Another term "hereditary hyperuricemia" represents only one of the genetically transmitted chemical abnormalities of the disease. Since the exact etiology of gout is unknown the term gout probably will be retained until further progress in the knowledge of the disease will lead to a better and etiologic denomination.

HISTORY

The clinical manifestations of the disease were well known to Greek and Roman physicians. The writings of Aretaeus of Cappadocia, Caelius Aurelianus and Hippocrates contain excellent clinical observations on gout, e.g., Aretaeus observed that during a remission a gouty individual was capable of winning the Olympic games.

Strict differentiation of gout from other joint diseases was attempted by Sydenham¹—who was himself afflicted with the disease for the major part of his life—in the classical "Tractatus de Podagra et Hydrope" (1683). The next century saw completely new aspects of the disease through discoveries in the field of chemistry. Scheele (1776) found uric acid to be a constituent of kidney stones² and twenty years later

* Friday Afternoon Lecture at The New York Academy of Medicine, Jan. 9, 1949.
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TABLE I—HISTORICAL REVIEW

Sydenham	1683	Differentiation of gout from other joint diseases
Scheele	1776	Identified uric acid in a kidney stone
Wollaston	1797	Discovered uric acid in tophi
Pearson	1798	Discovered uric acid in tophi
Garrod	1848	Discovered hyperuricemia—"Thread Test"
Miescher	1871	Nucleoproteins and nucleic acid in cell nuclei
Kossel	1879-1891	Purines are building stones of nucleic acid
Fischer, Emil	1907	Chemical structure of uric acid and purines
Folin	1913	Method for uric acid determination in blood
Blauch and Koch	1939	Method for determination of "true uric acid" with uricase

Wollaston (1797), and Pearson (1798) discovered the presence of uric acid in the tophi of individuals afflicted with gout.³⁻⁴ It was almost exactly one hundred years ago that Garrod (1848) established hyperuricemia as a feature of gout.⁵ With the famous "thread test" he discovered increased amounts of uric acid in the blood of gouty individuals. After Miescher (1871) had studied the role of nucleoproteins and nucleic acid in the cell nuclei⁶ and Kossel (1870-1891) the role of purines as building stones of nucleic acid,⁷ Emil Fischer (1907) established the chemical structure of uric acid and its relationship to that of purines.⁸

The important function of disturbed purine metabolism in gout was further elucidated by numerous clinical studies which were made possible by the introduction of reliable clinical methods for the estimation of uric acid concentration in the blood by Folin (1913)⁹ and later by modifications by Benedict (1931)¹⁰ and Folin (1934).¹¹ Although these methods did not specifically determine uric acid they were extremely helpful in metabolic studies of gout. The newer methods¹²⁻¹⁴ avoid the inclusion of other substances giving the same color reaction as uric acid by employing specific enzymes, uricases, for the determination of "true uric acid."¹⁵⁻¹⁸ Table I briefly summarizes the historical developments in gout.

In the following discussion only a few problems of gout will be presented: 1) Status of uric acid in the blood (uric acid partition), 2) hereditary hyperuricemia and its relation to disturbed lipid metabolism, 3) allergic factors in gout.

STATUS OF URIC ACID IN THE BLOOD (URIC ACID PARTITION)

Garrod attributed gout to diminished elimination of uric acid by the diseased kidney.⁵ There is, however, no evidence of renal disease or impaired kidney function in gouty individuals who have suffered several or even many acute attacks of gout, although in the late course of the disease renal damage, hypertension and azotemia may complicate the clinical picture. On the other hand, uric acid clearance of gouty individuals with high uric acid levels in the blood is lower than that found in individuals with hyperuricemia due to other diseases, e.g., leukemia. In normal subjects injection or ingestion of urate markedly enhances the clearance and results in rapid excretion of uric acid. In gouty subjects these processes are retarded and the recovery of administered uric acid is often not possible. The diminished elimination of uric acid might be caused by a specific impairment of renal mechanisms responsible for uric acid excretion. Especially in early cases of gout a specific renal defect of this sort is unlikely. All evidence points to retention of uric acid in the blood and in the tissues and possibly to an abnormally functioning fixation mechanism as a cause of the diminished elimination by the kidney. Impaired kidney function, present in later stages of the disease, is demonstrable with our proven kidney function tests and then represents a superimposed factor which causes with retention of various substances in the blood, additional retention of uric acid.

The problem of solubility of uric acid and urates in body fluids has been the subject of many studies. Uric acid is weak and dissolves in water in small amounts only. Sodium urate is more soluble¹⁹ but its solubility is depressed by the addition of sodium chloride. A physiologic solution of sodium chloride dissolves only one tenth of the amount soluble in distilled water.²⁰ The solubility of sodium urate in body fluids is much higher, however, than the determination of its solubility in physiologic solution of sodium chloride would suggest. Sodium urate solutions are characterized by properties specific for colloidal solutions such as opalescence, gel formation and the Tyndall phenomenon.^{21,22} This observation precipitated a discussion as to the existence of a colloidal form of uric acid in body fluids.^{23,24}

Regardless of certain controversies about the colloidal state of uric acid, clinical observations years ago led to the assumption of "free" and

"bound" uric acid. It was Minkowski²⁵ who first postulated the existence of combined uric acid in blood. Benedict and his co-workers²⁶ succeeded in isolating a compound of one molecule of uric acid with one molecule of dextrorotatory ribose from the blood of various species of animals and from human blood. It was assumed that this substance derives either from inosinic acid by oxidation of the hypoxanthine component or from guanylic acid by oxidation of the guanine moiety. This is the only organic combination of uric acid in the animal body the existence of which has been definitely proved.²⁷

A few French authors attempted to differentiate free uric acid from combined uric acid.²⁸⁻³⁰ Chabanier, Lebert and Lobo-Onell,²⁹ employed compensatory dialysis and concluded that all uric acid in the blood was free, as it was entirely dialyzable.

The question as to the colloidal and the bound state of uric acid in serum has not been settled by studies of uric acid clearance. Brøchner-Mortensen³¹ expressed the belief that uric acid in the blood does not exist in a colloidal or combined form but that it is a true threshold substance, completely excreted by the glomeruli and probably partly reabsorbed by the tubules. Berglund and Frisk³² however, assumed that part of the uric acid is in a nonfiltrable form, that only the free uric acid passes the kidney and that no reabsorption from the filtrate occurs.

Adlersberg, Grishman and Sobotka,³³ studied the partition of uric acid under normal and under pathologic conditions. The first series of experiments were performed with dialysis. Sera containing normal and elevated amounts of uric acid were dialyzed in cellophane bags. The uric acid was found to be completely dialyzable and the observation of Chabanier, Lebert and Lobo-Onell²⁹ could be confirmed. Essentially the same results were obtained in normal subjects after intravenous injection of uric acid which considerably raised the uric acid level of the serum. By subsequent exposure of these serum specimens to dialysis the uric acid was completely removed or traces of less than 0.04 mg. per hundred cubic centimeters remained. Apparently the equilibrium between free and combined uric acid is labile and can easily be disturbed by various factors, e.g., dialysis. Dialysis first removes the available free uric acid; this disturbs the equilibrium, and more uric acid is liberated, becomes dialyzable and is in turn removed from the serum. Hence, dialysis is not suitable for the study of uric acid partition in protein-containing fluids.

TABLE II—URIC ACID PARTITION IN NORMAL SUBJECTS AND IN PATIENTS WITH GOUT

	URIC ACID MG. PER 100CC. OF SERUM			
	<i>Total uric acid</i>	<i>Filtrable fraction</i>	<i>Non-filtrable fraction</i>	<i>Bound uric acid in % of total</i>
Normal Subjects.....	2.6—6.8 (5.0)*	2.2—5.8 (4.2)	0.2—1.3 (0.8)	4—24 (16)
Gout (10 pat.).....	5.1—16.4 (9.2)	1.9—14.4 (7.4)	0.1—3.6 (1.8)	1—65 (20)

* Figures in parentheses are averages.

Satisfactory results were obtained by the use of ultrafiltration. The range of the total uric acid, the ultrafiltrable and the non-ultrafiltrable fractions was established by a series of determinations on normal subjects. The uric acid content of the serum varied from 2.6 to 6.8 mg. per hundred cubic centimeters. The ultrafiltrable fraction of the serum uric acid ranged from 2.2 to 5.8 mg. per hundred cubic centimeters, with an average of 4.2 mg. The nonfiltrable or bound uric acid ranged from 0.2 to 1.3 mg. per hundred cubic centimeters, with an average of 0.8 mg. Expressed in percentage of the total uric acid, the bound uric acid averaged 16 in normal subjects, with a range from 4 to 24 (see Table II).

The uric acid partition in patients with various pathologic conditions was subsequently examined. All important disease groups were included, such as pulmonary, cardiovascular, renal, and hepatic diseases; diseases of the blood, as well as conditions known to be associated with disturbance of purine metabolism, such as gout, uremia and forms of leukemia. It soon became evident that hepatic disease and gout may produce an anomalous picture. Normal values for total, as well as for bound, uric acid were encountered in acute cellulitis, typical allergic bronchial asthma, nephrotic hypoproteinemia, with total protein values varying from 3.4 to 5.2 Gm, per hundred cubic centimeters and with inversion of the albumin-globulin ratio, in diabetes with and without ketosis. Elevated values for total uric acid were associated with a normal partition in uremia with marked azotemia, in lymphatic leukemia, myeloid leukemia, myasthenia gravis and amyotrophic lateral sclerosis.

The serum uric acid partition in patients with exophthalmic goiter

was normal except in a patient, whose case history was published elsewhere, who suffered from a peculiar form of persistent hyperthyroidism or possibly a hypothalamic lesion, who exhibited active symptoms of the disease in association with unusual muscular disturbances.³³ In contrast, two other patients with exophthalmic goiter, before and during medication, showed a normal uric acid partition. Marked deviation from the normal figures both for total and for bound uric acid was observed in a man with multiple myeloma. The serum of this patient was of syrupy appearance and of abnormally high viscosity. The total protein content was 11.6 Gm. per hundred cubic centimeters, with 3.2 Gm. of albumin and 8.4 Gm. of globulin. The total uric acid content was 8.6 to 9.8 mg. per hundred cubic centimeters, the bound uric acid ratio, on two occasions, 36 and 37 per cent, respectively. A second patient with this disease but without hyperproteinemia displayed a normal uric acid picture. With the exception of the two patients with atypical exophthalmic goiter and with multiple myeloma, the uric acid partition, in the pathologic conditions studied, did not deviate from that of normal persons.

Changes in uric acid metabolism have frequently been reported in patients with hepatic disease.^{34,35,36} In our own series,³³ a low titer of uric acid in the blood was met with only in patients with icterus of long duration and possible secondary hepatic damage (carcinoma of the pancreas, cholangitis with pylephlebitis). Patients with hepatitis and cirrhosis of the liver presented no consistent change in the total uric acid content of the blood, although in some instances they exhibited alterations of uric acid partition mostly in association with exacerbation of the disease. A group of patients with cirrhosis of the liver showed in the course of their illness normal figures changing into abnormal ones or vice versa. Thus, the value of 27 per cent bound uric acid in one patient decreased to 7 per cent within one week; the change was accompanied by clinical improvement. In contrast, another patient with cirrhosis of the liver started with a normal uric acid partition, and then, during the progressive deterioration of his general condition, which eventually led to a fatal outcome, showed gradual elevation of the bound uric acid ratio. Similarly, in some instances of hepatitis, normal values for total uric acid were associated with abnormal uric acid partition (up to 41 per cent bound uric acid). At the height of the disease and impairment of hepatic function, a disturbance of uric acid partition

prevailed, while uric acid partition was normal at the onset and during recovery. However, the material studied did not permit definite conclusions as to the relation between hepatic function and uric acid partition.

Ten patients with typical gout were studied. The levels of total uric acid in the serum of these patients were markedly elevated and varied from 5.1 to 16.4 mg. per hundred cubic centimeters; the average for all patients was 9.2 mg. per hundred cubic centimeters, almost double the average value for total uric acid in the serum of normal persons. The high level of the total uric acid was associated with an elevation of the free uric acid to 14.4 mg. per hundred cubic centimeters, with an average of 7.4 mg. The bound uric acid ranged between 0.1 and 3.6 mg. per hundred cubic centimeters, with an average of 1.8 mg., which was double the average bound uric acid in normal persons (see Table II).

Several observations of patients with gout will be briefly cited to illustrate the correlation of the findings with the clinical course. One patient had considerably elevated total uric acid levels (10.0 to 11.6 mg. per hundred cubic centimeters); the uric acid partition was fairly constant, the bound uric acid was 12 to 17 per cent of the total uric acid. Only on one occasion, during an attack of gout, was there an elevation of the bound uric acid to 24 per cent of the total uric acid. On initiation of colchicine therapy the symptoms promptly subsided, and two days later and thereafter the uric acid partition was normal. The elevation of the "bound" level simultaneously with the attack was of interest, although the value of 24 per cent bound uric acid falls just within the upper limit of normal. Similar elevations of the bound uric acid fraction were observed in other gouty individuals prior to or in early stages of an acute attack. A correlation of this phenomenon with the well known preparoxysmal diminished excretion of urinary uric acid might be considered.

Another patient with gout was never completely free of symptoms during the period of observation. Although the total uric acid content of the serum was high normal (5.5 to 5.8 mg. per hundred cubic centimeters), the uric acid partition was abnormal (26 to 65 per cent of bound uric acid). It is noteworthy that in this patient with typical gout a normal total uric acid content was associated throughout the period of observation with an abnormal uric acid partition. Another patient presented a similar picture, normal values for the total uric content (4.1 to 6 mg.

per hundred cubic centimeters), but an abnormal bound uric acid ratio of 27 to 33 per cent. On the other hand, hyperuricemia, even of an extremely high degree (13.0 and 16.4 mg. per hundred cubic centimeters), was associated in two patients with a normal uric acid partition (18 and 12 per cent, respectively) during the symptom-free period.

In several observations, colchicine resulted in lowering of the bound uric acid fraction without altering the total uric acid content. We surmised that the therapeutic effect of this drug in gout may be in some way connected with the "liberation" of uric acid in the blood and in the tissues.

The observations may be summarized as follows: Comparatively constant uric acid partition of the blood serum is characteristic of the normal individual. In pathologic conditions, gout and hepatic damage bring about disturbance of the uric acid partition, characterized by a diminution of the free, and elevation of the protein-bound, uric acid fraction. The liver is known to play an important role in protein as well as in purine metabolism; hence, hepatic disease may result in disturbances of this metabolic domain. In gout, the abnormal fixation of uric acid in blood and tissues might explain the retention and diminished elimination of this substance by the kidney.

The results of our studies on uric acid partition were confirmed and extended in observations by Wolfson, Levine, Tinsley and Huddleston.¹⁵⁻¹⁸ These authors analyzed the "total uric acid" of the plasma as well as the "true uric acid" (the amount of uric acid destroyed by uricase). The difference between total and true uric acid was attributed to chromogenic substances similar to those giving the color reaction for uric acid in plasma. Seventy-nine per cent of the plasma total urate and 77 per cent of the plasma true urate proved to be ultrafiltrable. In other words, 21 per cent and 23 per cent of the plasma urate, respectively, was bound urate, bound to plasma proteins. On the basis of these results and additional studies of uric acid clearance in man, Wolfson et al assume that the major portion of the plasma urate circulates in the form of polymeric urate complexes. Studies in normal and azotemic chickens added support to this hypothesis. However, it must be recalled that in birds uric acid is the chief end product of protein metabolism, analogous to urea in mammals, and therefore extreme caution is indicated in transferring these results to man. This conservative attitude is fully observed by Wolfson et al.

HEREDITARY HYPERURICEMIA: ITS RELATIONSHIP TO A
HEREDITARY DISTURBANCE OF LIPID METABOLISM
(HEREDITARY HYPERCHOLESTEROLEMIA)

There is increasing interest among clinicians in human genetics and in the early detection of carriers of hereditary disease. Talbott³⁷ observed hyperuricemia in 25 per cent of the relatives of patients suffering from gout. Stecher and Hersh^{38a} studied a group of thirty families, parents, siblings and offspring of gouty individuals. On the basis of numerical tests, they determined the mode of inheritance, the gene frequency, and penetrance. Smyth, Cotterman and Freyberg^{38b} studied 87 relatives of 19 gouty male patients. Hyperuricemia in these families was apparently due to a single autosomal dominant gene, but only a fraction of the heterozygotes for this factor developed manifestations of gouty arthritis. Sex and age were also important factors determining the level of serum urate (see also, Smyth, Stecher and Wolfson^{38c}). "The gene for essential hyperuricemia must be considered more common than one might suspect from the incidence of clinical gout."

We were particularly interested in these studies because of the relationship that apparently exists between hereditary hyperuricemia and hereditary hypercholesterolemia. In previous publications^{39a, b, c} attention was called to the fact that familial xanthomatosis is not a rare disorder. It has long been so regarded because its two most striking external manifestations, xanthoma tuberosum and xanthoma tendinosum are met with infrequently. In a study^{39b} of 35 xanthoma families comprising 172 members and an additional 29 individuals belonging to such families (total 201 persons), only 49 (24 per cent) exhibited the full syndrome, i.e., hypercholesterolemia, coronary artery disease and either xanthoma tuberosum or tendinosum or xanthelasma or corneal arcus. Elevation of serum cholesterol (to 300 mg. per cent or more) was found in 69 per cent of the examined individuals, coronary artery disease in 40 per cent. Xanthelasma of lids was present in about 30 per cent. Tuberos or tendinous xanthoma was present in only 12 per cent and all of these individuals had hypercholesterolemia excepting two whose cholesterol was unknown. Thus, the two most frequent abnormalities encountered among members of xanthoma families were hypercholesterolemia and coronary atherosclerosis; xanthelasma of the lids and corneal arcus were next in frequency, while xanthoma of skin or ten-

dons was least often found. Genetic analysis of the families supported the concept that the involved disturbance of cholesterol metabolism is inherited as an "incomplete" dominant trait.^{39b}

The results obtained in the study of xanthoma families were compared with those of 122 unselected patients with proved coronary artery disease under age of 50 of whom seventy-one (58 per cent) had hypercholesterolemia.^{39c} Fifty families of these patients were available for study. In fifteen families, all or most siblings exhibited hypercholesterolemia (300 mg. per cent or more) and in nine families one-half of the siblings showed this disturbance of cholesterol metabolism. Many siblings also exhibited xanthelasma and corneal arcus and a few xanthoma. Genetic analysis of these sibships by Stecher and Hersh⁴⁰ revealed that the number of individuals with hypercholesterolemia fitted a 1:1 Mendelian ratio and that hereditary transmission probably took place as a dominant trait.

Consideration of all data^{39a, b, c} led to the concept that the common factor for younger individuals with coronary atherosclerosis may be a hereditary error of cholesterol metabolism. Familial xanthomatosis is then the most severe form of the inborn metabolic disturbance. Xanthoma lesions develop only in patients who carry two abnormal genes for cholesterol, i.e., are homozygotes. Atherosclerosis is frequent in such individuals. Many patients with uncomplicated coronary artery disease are probably affected with a milder form of disturbed lipid metabolism. They carry one abnormal gene for cholesterol, i.e., are heterozygotes. Derangement of cholesterol metabolism may help to explain the familial incidence of coronary artery disease and may also account in part for its development in many persons under 50 years of age.

Hypercholesterolemia may prove to be an inborn error of metabolism similar to gout, albinism or cystinuria, which are definitely dependent upon genetic factors.^{40, 41} Since hereditary hyperuricemia and hereditary hypercholesterolemia apparently represent somewhat similar inborn errors of metabolism, it seemed profitable to study members of families exhibiting hereditary hypercholesterolemia for evidence of hyperuricemia. Actually, simultaneous occurrence and overlapping of both metabolic abnormalities was a not infrequent occurrence. Approximately one-third of our original patients showed both hypercholesterolemia and hyperuricemia.^{39a} Since then, we have observed a number

of additional individuals, who showed both abnormalities without any evidence of clinical gout or renal disease.

Table III presents the data of 27 individual members of hypercholesterolemic families, whose serum cholesterol ranged from 250 to 870 mg. per one hundred cubic centimeters, average 452 mg. The uric acid concentration of the serum ranged from 2.5 to 9.4 mg. per one hundred cubic centimeters. A breakdown of these figures reveals that one-third of these persons exhibited hyperuricemia (levels above 6 mg. per one hundred cubic centimeters, range 6 to 9.4 mg.), one-third had borderline levels of 5 to 6 mg., and the rest had less than 5 mg. Interestingly enough, there were no clinical manifestations of gout (gouty arthritis) in the individuals who exhibited hyperuricemia. Wolfson⁴² confirmed these observations and termed the syndrome: "Non-gouty hyperuricemia associated with familial hypercholesterolemia."

The coincidence of the two metabolic errors concerning purines and lipids may prove of importance in future studies of the underlying mechanisms which as yet are completely obscure. It is established that diets high in lipids result in diminished elimination of uric acid even in normal individuals,⁴³ an important fact to be remembered in the planning of diets for patients with gout. Following injection of adrenocorticotrophic hormone of the pituitary (ACTH) there is a marked decrease of esterified cholesterol in the adrenals and an increased urinary excretion of uric acid. These well-established observations suggest closely related endocrine regulatory mechanisms of the cholesterol and uric acid metabolism by the pituitary-adrenocortical system. The occurrence of hyperuricemia and hereditary hypercholesterolemia in the same individual adds a new link to the relationship that exists between the metabolism of purines and that of lipids. Studies of genetic patterns of hyperuricemia in these families are in progress. Furthermore, investigation of adrenal cortical hormones in both gout and hereditary hypercholesterolemia may help to establish the possible function of the adrenal cortex in these disorders.

ALLERGIC FACTORS IN GOUT

The sudden onset of the acute attack in gout and the full restitutio ad integrum, at least in the early phases of the disease, resembles an anaphylactic or allergic phenomenon.⁴⁴⁻⁴⁷ Experienced clinicians always attributed great importance to certain foods and beverages, especially

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BULLETIN OF THE NEW YORK
ACADEMY OF MEDICINE

CONTENTS

A General View of Cancer Research 671
Leonard A. Scheele

An Evaluation of the Surgical Treatment of
Hypertension 698
R. H. Smithwick

Recent Advances in the Therapy of the More Common
Protozoan and Helminthic Infections of Man . . 717
Harry Most

The New York Academy of Medicine:
Its First Hundred Years—Philip Van Ingen . . . 741
A Review—*Mablon Ashford*

Report of Subcommittee on
Proposed Hospital Bond Issue 743 ✓

AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

MAHLON ASHFORD, *Editor*

Published Monthly by THE NEW YORK ACADEMY OF MEDICINE
2 East 103 Street, New York 29, N. Y.

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE



NOVEMBER 1949

A GENERAL VIEW OF CANCER RESEARCH*

The Fourth James Ewing Memorial Lecture

LEONARD A. SCHEELE

Surgeon General, U. S. Public Health Service, Federal Security Agency

SOME years have passed since cancer patients and the medical profession last benefited by direct association with Dr. James Ewing. Yet those who knew him (and there are many of us present who did) surely retain a vivid impression of his personality and genius, which seem to transcend time. My words could add nothing to your experience. Those who did not have the fortune of his acquaintance may know him as a legend—as one who devoted the major part of his life to the study and diagnosis of cancer; as scholar, author, teacher; and as one of the scientific founders of Memorial Hospital. Such a conception is a true one. But legendary figures, as they grow in repute, may dwindle in humanity—become less real. So rather than discuss his work, I should like only to say, of the man himself, that James Ewing was intensely human—incisive, sincere, altruistic—one who sought truths, and found them, in the study of human nature as well as disease. No lines in epitaph could be more fitting than those of Lowell:

Great truths are portions of the soul of man;

Great souls are portions of eternity.

* Delivered at the Stated Meeting of The New York Academy of Medicine, May 5, 1949.

NATIONAL CANCER INSTITUTE RESEARCH GRANT FUNDS APPROVED IN RELATION TO THOSE REQUESTED BY REGION

1937 THROUGH APRIL 30, 1949

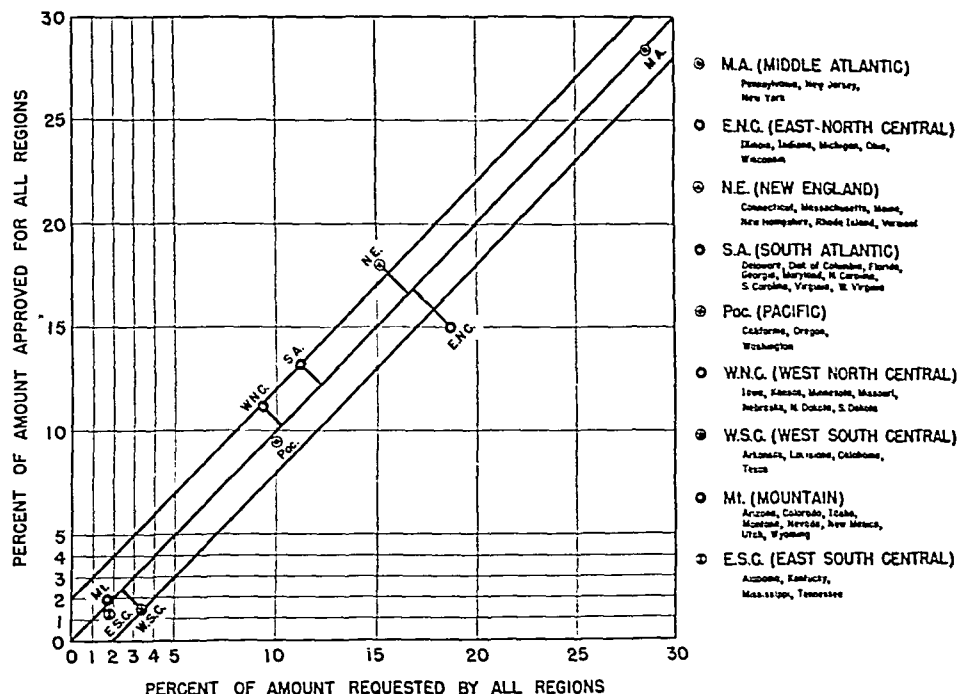


Chart 3

The growth of the grant-in-aid program is represented in Chart 1. Each black bar shows the total amount granted that year for cancer research in nonfederal institutions, and the shaded bars represent the amounts awarded for research fellowships. It should be pointed out that the bars represent projects started each year, and taken singly do not necessarily reflect annual Congressional appropriations, though in the aggregate they do. Research fellowships are awarded to increase the number of scientists trained in disciplines through which the cancer problem can be attacked. On the first of May 1949, there were 100 National Cancer Institute research fellows in active training in the United States and abroad.

Chart 2 presents a geographic distribution of cancer research grants and requests since the inception of the program. Other data indicate that this material reflects, quite accurately, the distribution of all

THE PROGRAM OF THE NATIONAL CANCER INSTITUTE

Total Appropriation 1948-49, \$22,000,000

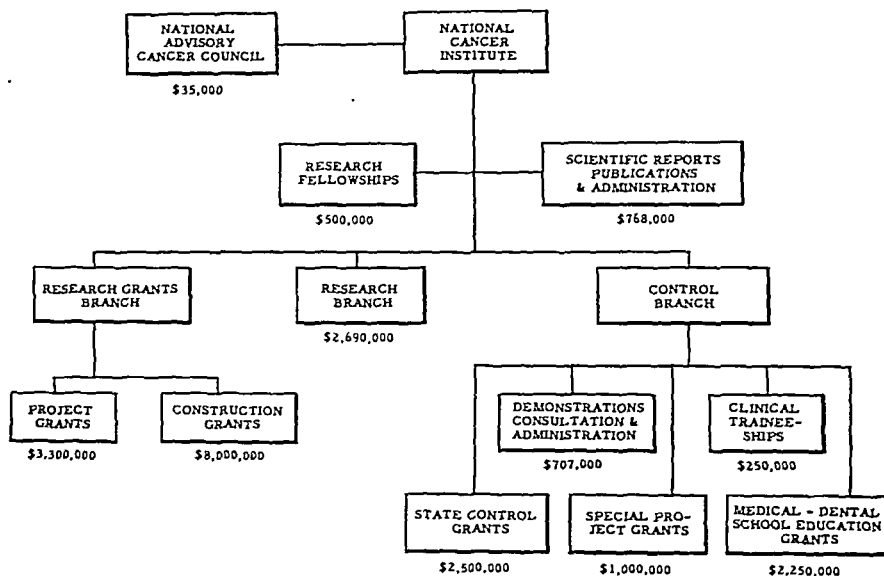


Chart 4

cancer research and 'research potential' throughout the country. For the past two years, grants for the construction of research facilities (not shown in this chart) have helped to increase the research potential of the less active areas.

The same data were used in preparing Chart 3, which presents a comparison of the amount awarded and that requested, by region. Only the applications the Council has acted on are represented: some requests have been withdrawn and a few await further investigation. The proximity of plotted points to the diagonal line reflects a nearly constant ratio of approved to requested grants.*

In 1947 the National Cancer Institute was reorganized to provide for effective integration of a much-expanded program. Chart 4 shows the allotment of appropriation for the fiscal year 1949. It shows that the activities of the Institute are administratively divided into three major fields—research grants to outside institutions, scientific research

* Deviation is greatest for the Southwest, which made only a few applications, and those for large sums.

within the Institute, and cancer control. Of the total appropriation of \$22,000,000 for this year, more than half, \$11,300,000, has been allocated for research grants—\$8,000,000 of that, for construction of cancer research facilities. About twelve per cent of the total appropriation, \$2,690,000, will be spent on intramural research; and about thirty per cent, \$6,707,000, on cancer control.

If these activities were presented in detail, they would illustrate the breadth of the cancer research field—the diversity of approaches, the multiplicity of disciplines applied to fight this disease. No stronghold against science is under a more varied attack. In the remainder of my paper, I have tried to present a general view of the scientific problem posed by cancer. And now, in the hope that this view will be of interest, I should like to discuss in relatively nontechnical terms, the investigative aspects of cancer research.

Pasteur, in defining *science*, wrote that it is “built up of successive solutions given to questions of ever-increasing subtlety, approaching nearer and nearer towards the very essence of phenomena.”¹ This statement seems especially applicable to cancer research. Nearly every method whereby other diseases were controlled has been tried—serologic techniques, the search for a microörganism, a decisive dietary factor, a curative drug. Some of these approaches, of course, still hold promise; but refinements inconceivable to the early workers seem necessary. We must continue to answer “questions of ever-increasing subtlety.”

Consider, for instance, the matter of etiology. With the discovery, in many diseases, of a causative microörganism or its vector, the problem of control was well in hand. Other diseases were found to result from a dietary deficiency, and still others followed a simple genetic pattern. For all practical purposes, the discovery of a cause closed the question of etiology. In the study of cancer, however, investigation has disclosed a gamut of etiologic agents and influences. Let me enumerate briefly: energy agents, such as X-rays, radioactive substances, ultraviolet rays, and heat; more than 300 chemical compounds; viruses; parasites (which may be vectors for viruses); endocrine and dietary manipulations; and multiple genetic factors.² We are at liberty to regard cancer as one disease with a variety of possible causes, or as a number of diseases.

To know ways to produce cancer is by no means to have found ‘the cause,’ for most tumors are not attributable to known carcinogens.

And if subtlety is in order, it may be said that the purpose of studying cancer etiology is no longer to find the cause, but to *explain the origin*.

A large part of cancer research in this country and abroad is devoted to the study of tumor genesis and early development, since elucidation of these processes would, in all probability, lead not only to preventive measures but also to improved diagnosis and therapy. This may be the long way, but it seems sure. In discussing studies of origin and development, I shall observe a broad classification into fundamental biologic investigation and studies of carcinogenic agents and influences.

Although the term *cancer* is usually associated with a complex of phenomena, including invasion, metastasis and other aberrations of growth, the most prominent characteristic of the disease is the excessive, inexorable proliferation of cells. That characteristic is well recognized: I mention it only to illustrate that cancer is a disease of the mechanism whereby tissues are formed or replenished—the forces controlling the type of cells engendered and the direction and cessation of growth. In this light we see clearly the importance of investigating basic biologic processes, such as cell division, differentiation and adaptation.

In recent years the intracellular movements involved in mitosis have been investigated in terms of tension resulting from changes in the viscosity of protoplasm. Studies by Chalkley, Marsland and others indicate that cell division depends, to some extent, upon colloidal fluctuations between sol and gel.³ One can hope that the fluctuations will in turn be explained. But the problem, it would seem, approaches a basic physical level, where it can be studied in terms of factors affecting colloids, such as pressure, temperature and chemical composition.

During the past decade, the intracellular microcosm has been under exploration with the electron microscope, which is about a hundred times as powerful as previous instruments. Recent studies by Porter and others have disclosed entities that may represent the underlying structure of cytoplasm.⁴ In combination with ultracentrifugation, ultrafiltration and other newly developed techniques, the electron microscope may yet reveal characteristics of the cancer cell that will elucidate its origin and activity.

The processes of differentiation and regeneration are studied because of possible similarities to carcinogenesis and subsequent anaplasia. Both differentiation and carcinogenesis apparently result in a new type of cell. The former process, however, is consistent with the total pattern

of cellular organization—it is controlled; whereas in carcinogenesis, the part defies the whole. The processes may also differ in direction: that is, the cells in differentiation become, as a rule, more specialized; whereas in tumors they seem to dedifferentiate, to form tissues more like each other, morphologically and chemically, than were the tissues of origin.^{5,6} It appears, however, that dedifferentiation may also occur in noncancerous development. In lower forms such as Amphibia, regeneration, as in a healing wound, is reported by Rose to involve dedifferentiation as a primary stage;⁷ and in tissue culture morphologic simplification has been observed by Fischer and others in cells of even higher vertebrates.⁸ Whether controlled dedifferentiation occurs, however, *in vivo* in higher animals, such as man, is still unknown.

To explain the relation of differentiation to cancer, much basic information is needed. We should like to know, for instance, whether the level of differentiation influences susceptibility of the cell to carcinogens. Clarification of the identity and role of 'organizers' would be valuable. In these and other basic biologic investigations, lower forms lend themselves well to study: the planarian, noted for its remarkable ability to regenerate a head; the hydra, whose cells after passage through a strainer will reassemble to form whole animals; the platy fish [*Platy-poecilus*], because of its wide regenerative capacity, its response to androgen, and its susceptibility to melanoma in certain hybrids. Studies of differentiation represent attempts to relate carcinogenesis to the source of cellular variation, a process of which far too little is known.

One type of cellular variation is represented in adaptation to an unfavorable environment. Many scientists believe that all living organisms, including the cells of a multicellular species, are endowed with a capacity to adapt. This suggests a point of view from which cancer may be regarded. Carcinogenesis may be the manifestation of an attempt of cells to survive through adaptation. From the standpoint of the host, cancer certainly represents the antithesis of a tendency toward survival; but we cannot deny that a cancer cell, among its normal neighbors, is an exalted being. And one could add that its destruction of the host does not debase the concept: some microorganisms do the same. Experiments by Spencer^{9,10} suggest that processes similar to some found in cancer occur in single-cell species exposed to carcinogens over many generations. Exposure of paramecia to methylcholanthrene enhanced the subsequent survival value and population levels, and bacteria tended to

adapt to heat when early exposure was rhythmic, but perished when it was continuous. These transformations are readily accepted as adaptive.

In the field of basic biologic investigation, notable advances have been made recently by some of our workers in tissue culture. Earle and Evans at the National Cancer Institute have worked out a technique for growing cells under a sheet of perforated cellophane, which obviates the need for a plasma clot and affords much larger cultures than were previously grown.¹¹

A further accomplishment of this laboratory, by Earle and Sanford, is a procedure that allows, for the first time, the growth of an isolated cancer cell *in vitro*.¹² These techniques, in combination, make possible the growth of large cultures from a single cell, and consequently the cancer research worker can now study ample cultures of uniform cellular origin and type.

Obviously these achievements increase greatly the applicability and quantitative accuracy of tissue culture as a means of studying possible chemotherapeutic agents, carcinogenesis, and cell variation, migration and growth rate. The new techniques are already being used in an effort to define more accurately the nutrition of the cancer cell. The full potentiality of these advances, however, cannot be estimated at the present time.

A discussion of carcinogenic agents and influences may well begin with the subject of radiation, since the first experimental cancers in animals, such as Clunet¹³ reported in 1910, were induced with X-rays. On the basis of numerous experiments and clinical observations, investigators agree that ultraviolet and ionizing radiations are carcinogenic. The mechanism of radiation injury is only partly understood. Experiments indicate, however, that absorption of radiation causes chemical changes detrimental to cells and tissues. The biologic effect is to some degree cumulative. And therein lies the danger of repeated exposure, even to very small doses. In studies by Lorenz and others,¹⁴ chronic whole-body irradiation hastened the onset of cancer in mice predisposed to the disease, and late effects other than tumor production include shortening of the life span. X-ray diagnosis in the hands of a competent physician constitutes a justifiable exposure. The problem of radiation injury, however, is becoming more and more important with the increasing use of ionizing radiations in science and industry.¹⁵

TABLE I*—HIGHLIGHTS IN THE STUDY OF CHEMICAL CARCINOGENS

<i>Investigator</i>	<i>Contribution</i>
Pott (1775) _____	Reported soot-induced carcinomas in chimney sweeps
Yamagiwa, Ichikawa (1915)_____	Produced carcinoma of rabbit's ear with tar
Kennaway, Cook, Hieger (1930) _____	Isolated 3,4-benzpyrene from coal tar; synthesized other carcinogens
Shear, Andervont, Fieser, Lorenz, Stewart (1930—)_____	Studied administration and effects of carcinogenic hydrocarbons on animals of inbred strains
Wieland, Cook (1933)_____	Prepared 20-methylcholanthrene from desoxycholic acid
Yoshida, Sasaki (1934) _____	Produced hepatomas in rats with <i>o</i> -aminoazotoluene
Edwards (1941) _____	Produced hepatomas in mice with carbon tetrachloride
Wilson, De Eds, Cox (1941)_____	Noted multiple tumors in rats fed <i>N</i> -acetyl-2-aminofluorene
Nettleship, Henshaw (1943)_____	Noted that urethan increased lung tumors in pre-disposed mice
Berenblum (1941) _____	Discovered synergy of 3,4-benzpyrene and croton oil

* Material from Greenstein, J. P., *Biochemistry of Cancer*, New York: Academic Press, Inc., 1947.

Table I gives a thumbnail history of the chemical carcinogens. Sir Percival Pott is credited with the first report of industrial cancer.—During the 19th century, skin cancer was prevalent among workers in the coal tar industry; but many years passed before two Japanese workers proved experimentally that tar is carcinogenic.—The next step was to isolate a pure carcinogen, and this was finally accomplished through the perseverance of Kennaway's group in England.—As these workers produced other pure agents, a group established by Shear, under the United States Public Health Service, studied the carcinogenicity of compounds synthesized in this country, and for about a decade the two major efforts in the field overlapped.—In view of the next achievement listed (the preparation of a potent carcinogen from bile acid), one naturally wonders whether this or a similar transformation could occur in the body. Biochemists agree that *this* transformation is highly improbable; but the close structural relation of many carcinogens and

TABLE II*—HIGHLIGHTS OF TUMOR VIROLOGY

<i>Investigator</i>	<i>Source of Virus</i>	<i>Subject and Result</i>
Rous (1911) _____	Plymouth Rock hen, sarcoma	Same species, sarcoma
Ellerman (1918) _____	Chicken, leukemic blood	Same species, leukemia
Shope (1932) _____	Cottontail rabbit, papilloma	Cottontail, domestic rabbits; papilloma
Rous (1935) _____	Shope papilloma	Domestic rabbit, carcinoma
Bittner (1936) _____	Mice of high tumor strain, milk	Progeny, mammary carcinoma
Lucké (1938) _____	Leopard frog, carcinoma	Same species, carcinoma of kidney
Duran-Reynals (1942—)	Rous sarcoma	Duckling and other birds; variety of tumors

* Material from Oberling, C., *The Riddle of Cancer*, New Haven, Yale Univ. Press, 1944.¹⁶

naturally occurring substances, such as the steroid hormones, demands that the possibility of a similar conversion be considered.

—The next three lines represent the introduction of new groups of compounds.—Urethan, mentioned in the next to the last line, offers relative simplicity of structure, a decided advantage in tracer studies of the mechanism of carcinogenesis. Larsen, studying the structure of compounds of this type in relation to biologic response, found that the simplest alterations of the urethan molecule reduced activity fully 90 per cent. Urethan administered to pregnant mice induced lung tumors in the offspring.—And lastly, we have a clear-cut example of synergistic action between a carcinogen and a noncarcinogen, a phenomenon discovered about ten years ago by Shear, who showed that the basic fraction of creosote oil accelerated skin tumor production by various hydrocarbons. Berenblum, now at the National Cancer Institute on a Special Fellowship, has shown that the appearance of cancer in mice following application of benzpyrene, the 'initiator,' is markedly accelerated by croton oil, a noncarcinogen acting as 'promoter.'

Over the years much thought has been spent in searching the chemical and other carcinogens for a characteristic structure or mode of action—in short, a 'common denominator.' Perhaps the oldest and most

familiar deduction is the 'irritation hypothesis,' extant today in modified forms. The chemical carcinogens especially have been subjected to this analysis, which largely accounts for their multiplicity; but by and large, they remain in structurally unrelated groups. In recent years, emphasis in the search for a common denominator has shifted to the cell.

Table II outlines the study of virus tumors. Rous was among the first to succeed in transmitting cancer from one animal to another by means of a cell-free filtrate.* The Rous agent has increased in virulence with subsequent transfers, and will now induce cancer in chickens within five days after inoculation, about ten times as rapidly as the most effective of other carcinogens.—Ellerman, using filtrates of sera from fowl, transmitted leukemia within the species.†—The benign virus tumor found by Shope in the wild rabbit—was shown by Rous, Beard and Kidd to become malignant in domestic rabbits.—Next in the table is Bittner's demonstration that mice of a strain in which mammary carcinoma is ordinarily frequent develop few tumors if nursed by mice of a low-tumor strain, indicating that a factor of mammary tumor development in mice is transmitted by the milk. The history of the milk agent is too long and involved to review at this time.

—To my knowledge, the tumor of the frog shown by Lucké has not been transmitted by a cell-free inoculum, but results were obtained with grafts killed by storage in glycerol.—Lastly, Duran-Reynals's studies in virus variation: showing, for example, that the Rous agent, though innocuous to ducks, will 'take' in ducklings, and when recovered from a late tumor will then take in ducks, but will have lost capacity to induce cancer in chickens. In short, a tumor virus specific for one species may become specific for another, if closely related. It will be noted that in every example in the table (except that of the milk factor in mice) inoculation has been necessary to transfer the disease.

Round shadow-casting particles, believed to be viruses of the Shope papilloma, have been photographed by Kahler and others with the electron microscope. This agent cannot be recovered from the carcinoma it induces in the rabbit, though serologic methods have demonstrated its presence. It is said to be 'masked.' At present, one objective in tumor virology is to develop unmasking techniques, which would then be applied to other tumors in an effort to reveal a virus if one exists.

* Fujinami and Inamoto, at about the same time, reported cell-free transmission of a myxosarcoma of fowl.

† A similar disease in fowl, a malignant leukosis, is also attributed to a filterable agent, and recent studies by the U. S. Department of Agriculture indicate that leukosis may be contagious in birds."

TABLE III*—HIGHLIGHTS OF TUMOR ENDOCRINOLOGY

<i>Investigator</i>	<i>Contribution</i>
Marie (1886) _____	Associated cases of acromegaly with pituitary tumors
Loeb, Lathrop (1919) _____	Prevented mammary tumors in mice by ovariectomy
Lacassagne (1932) _____	Induced mammary tumors in mice with pure estrogen
Nathanson, Andervont (1939) _____	Prevented mammary tumors in adult female mice with androgen
Huggins (1940) _____	Treated prostatic carcinoma in men by control of androgen
Woolley, Little (1943) _____	Noted sex organ development through adrenal compensation in castrated mice
Biskind, Biskind (1944) _____	Noted development of tumors in rat ovary transplanted to spleen
Hertz, Tullner (1948) _____	Demonstrated quantitative interdependence of hormones and a vitamin in tissue growth

* Material from Greenstein, J. P., *Biochemistry of Cancer*. New York, Academic Press, Inc., 1947.

The Rous agent, because of its rapid, apparently direct action, is particularly useful in studies of carcinogenesis. Effective methods for quantitative assay of the agent have been worked out by Bryan at the National Cancer Institute.¹⁸ But a major obstacle remains—the lack of a method for extracting pure virus, needed for studies of mechanism. To develop such a method is a major objective in tumor virology today.

Now, in view of the fact that cancer research is ultimately concerned with human cancer, we may rightly ask: Why this deep interest in the virus tumors of animals? Simply because they offer valuable material for studies of carcinogenesis, which is probably a manifestation of the same intracellular derangement whatever the agent or species. In passing, let me emphasize that there is no accepted evidence of a virus cancer in man.

Table III lists some of the highlights of tumor endocrinology.* Pierre Marie, in associating a disease of endocrine origin with tumors of the pituitary, introduced a broad area of study and an important aid in cancer diagnosis. It was later established clinically that removal of an

* The material in this table, unless otherwise noted, is from Greenstein, *Biochemistry of Cancer*.¹⁹

endocrine gland tumor would often correct abnormalities of development.²⁰—Through use of mice predisposed to mammary cancer, Loeb and Lathrop demonstrated a hormonal factor in carcinogenesis, placing tumor endocrinology on a sound experimental basis.—In connection with the next study listed, it should be mentioned that Allen and Doisy were the first to isolate a pure sex hormone.—Nathanson and Andervont, by injecting androgen, reduced the incidence of tumors in estrogen-developed tissues; and Nathanson, Haddow, Adair and others subsequently showed the value of steroid hormones in the treatment of breast cancer.

—This work of Huggins is a triumph of biochemistry as well as endocrinology. After appropriate preliminary studies on dogs, Huggins, Stevens and Hodges succeeded in controlling, at least in a limited way, prostatic cancer in men by means of castration or estrogen administration. Moreover, the acid phosphatase levels of the sera, as shown by the Gutmans and others as well as by Huggins, proved to be highly accurate indices of case progress. Most patients are improved, and many show marked and prolonged remissions of primary and metastatic lesions.

—In the next study listed, the castrated mice developed a high incidence of adrenocortical carcinoma.—In the next study, the tumors were attributed to stimulation of the ovary by pituitary hormone, an effect normally counteracted by estrogen, which in this case was inactivated in the liver.

—Hertz and Tullner, at the National Cancer Institute, have demonstrated that folic acid is required for normal growth response to estrogen, and that folic acid antagonists can inhibit growth of estrogen-stimulated tissues. Dietary manipulations produced a 40-fold differential in estrogen-induced growth of the chick genital tract.²¹

When viewed chronologically these isolated achievements elude interpretation. I believe, though, that the findings warrant the following generalizations: first, some tumors are functional with regard to hormonal production or response; second, tumors may be induced, prevented or controlled by hormonal manipulation; third, derangement of endocrine relations within the body may result in cancer; and fourth, tissue growth normally supported by hormones may be inhibited by antagonists. Thus the importance of endocrinology in the etiology, diagnosis, and treatment of cancer is plainly revealed.

Dietary manipulations have been shown to exert pronounced effects

on carcinogenesis in animals. Caloric or amino acid restriction prevents or delays the appearance of a variety of tumors,²² and choline deficiency, on the other hand, results in the development of hepatomas in the rat.²³ It is doubtful that these observations are of immediate practical value: the cancer-preventing diets abolish breeding capacity, and choline occurs in a wide variety of foods. As leads in cancer research, however, these and similar findings are highly encouraging and offer many suggestions for further studies. In one promising line of investigation, chemical carcinogens are administered to animals in conjunction with dietary manipulations, permitting precise control of two variables. In these studies the azo dyes are especially useful, since their action is known to be a function of diet.²⁴

The effect of dietary alterations on human tumors already established has been relatively small in the few studies completed to date. In some animal experiments, however, alternate restriction and supply of a vitamin, such as riboflavin or pantothenic acid, has appreciably prolonged life, and further investigation is indicated.²⁵ Intensive studies on animals and selected cancer patients are needed before the role of nutrition in the control of cancer can be established.

In discussing the genetic influence in cancer, I will try to interrelate some of the material already published in this field. I believe that an understanding of the role of genetics in cancer must begin with a sound concept of the gene-character relation. Strictly speaking, a character, such as hair color, height, or color blindness, is not inherited. Its development is a result of the action of an inherited gene, or complex of genes, in a particular environment. The gene is a constant; the environment, a variable; the character, a product of the two. Stated otherwise, genes determine susceptibility to character formation; and with respect to cancer, may be said to establish, in every person, a threshold of susceptibility to the disease. The effective environment in character formation may include intra-uterine factors, diet, occupational influences—any condition, in fact, to which the individual is exposed; and it may include, secondarily, physiologic factors affecting cells. In plain words, then, cancer is not inherited, but a degree of susceptibility to it is.²⁶ And the adverse environment, whether that of the individual or a susceptible cell, is not beyond control.

The immediate questions confronting the geneticist in cancer re-

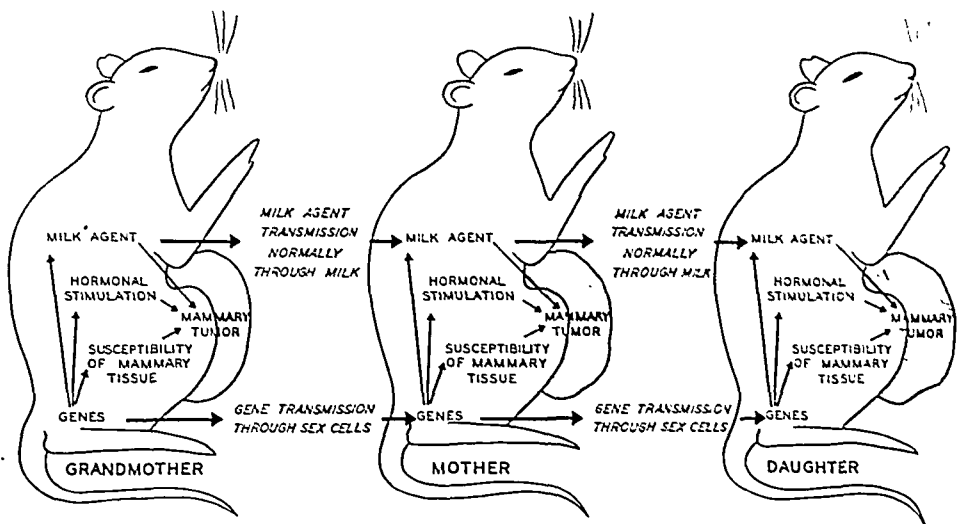


Figure 1—Relation of genes to other factors of mammary tumor development in the mouse

search are these: What are the genetic factors involved in carcinogenesis? To what environmental factors are they related? and By what physiologic paths do the genes function? For the most part, the problem is approached through studies with plants and lower animals, a practice well-grounded on the fact that the laws of genetics are among the most widely applicable in the field of biology. And of course the breeding rate must also be considered in studies involving several generations. An example of a lower form that has proved valuable as study material is the bread mold *Neurospora crassa*, which Beadle,²⁷ Tatum and others have used to disclose genetically controlled enzyme systems essential to the manufacture of protoplasmic constituents. Another useful species in cancer research is the common fruit fly [*Drosophila melanogaster*].

The most widely used subjects, however, are the mice of inbred strains, for which we are mainly indebted to the foresight of C. C. Little and the perseverance of L. C. Strong. Through inbreeding with selection over many years, geneticists have developed strains with high, predictable rates of cancer—mammary, lung, liver, etc.—and other strains in which tumors are infrequent. A high percentage of all cancer research requires these standardized experimental animals.

I have said that most cancers are not attributable to known carcinogens. This statement is more obviously applicable to tumors other than

mammary that arise in these mice, whose external environment throughout life is apparently normal—that is, noncarcinogenic. We may assume that these mice have a high concentration of genes favorable to tumor development; but cancer is the product of genes and environment. How, then, can we explain that the over-all incidence of cancer in some strains may be higher than 80 per cent? Speaking generally, suspicion centers on the following possible environmental factors: one, a transmissible agent, of external or internal origin; two, a carcinogenic constitutional pattern, perhaps a result of intra-uterine effects on organization; and three, a combination of these.

Such a combination has been shown to constitute the effective environment in mammary tumor production in the mouse. Figure 1, prepared from material developed by Heston, represents the genes as determinants of the constitutional pattern as well as the susceptibility of the mammary tissue.²⁸ The cancer-predisposing constitution, in itself a product of genes and environment, operates in this case through hormonal stimulation of the tissue and propagation and transmission of the milk agent. It is highly encouraging that cancer in these mice, though the genetic influence is strong, can be prevented by foster nursing or endocrine control.

The question naturally arises, To what extent can these genetic findings be applied to cancer in man? On the basis of these and other studies, we can certainly say that hereditary factors are involved, and that these are related to environmental factors.²⁹ Perhaps our most important gain from this work is a conception of the probable nature of the carcinogenic influences in human cancer of unknown etiology.

We have all heard, but it bears repeating, that there is no evidence for a milk agent in human beings. Indeed, there is statistical evidence against it, in that studies have failed to reveal a higher incidence of breast cancer among the female ancestors of mothers than among those of fathers of breast cancer patients.³⁰ At present, practical application of our knowledge of the milk agent is not indicated. But the search for similar factors in human cancer must be continued.

Since man is not inbred, nor reared under laboratory conditions, one cannot predict—even if both parents have cancer of the same organ—whether the offspring will develop the disease. The genetic factors of most types of cancer are probably multiple. This and practical difficulties preclude eugenic control.²⁸ Further genetic studies, however,

may disclose environmental and hereditary factors of cancer in man as they have in animals.

The development of genetically pure strains of mice, tumor transplantation techniques, and dependable means of inducing experimental cancer has made possible the productive application of biochemical methods in cancer research. In little more than a decade, biochemical analysis, performed against a background of biology, biophysics, pathology and other disciplines, has greatly contributed to an understanding of the properties of tumors and the tumor-bearing host. Whereas previous investigation was largely concerned with describing tissues in terms of composition, present biochemical studies emphasize the elucidation of tissue function—in a word, metabolism. And in view of the fact that cancer is a problem of growth, the importance of the new science in cancer research is manifest.

I shall attempt only to touch upon some of the major areas of activity in this field. Emphasis is placed upon those aspects of metabolism that would seem instrumental in the origin or maintenance of neoplasia: namely, enzyme activity, which underlies and effects the metabolic processes; protein synthesis, which in tumors is obviously excessive; carbohydrate utilization, which is glycolytic and hence supplementary; and the role of nucleic acid, which is associated with cellular reproduction.

With regard to enzyme activity, it may be said that every type of tissue is equipped with a characteristic pattern of enzymes, which serve as catalysts in metabolic reactions. The enzyme patterns of normal tissues are highly differentiated and vary markedly from one tissue to another. Greenstein has shown that in tumors, on the other hand, the patterns tend to be undifferentiated and nearly uniform, resembling those of the normal embryo.⁶ This may explain how tumor tissue, though apparently devoid of a special 'cancer enzyme,' is geared for speed. Fundamental enzymology must be emphasized in any comprehensive program of cancer research.

In the study of tumor metabolism, untold possibilities are afforded by the recently developed techniques of tracing tissue components tagged with stable or radioactive isotopes. The major objective in tracer studies of protein synthesis is to explain the mechanism whereby substances that enter the metabolic processes are utilized in the formation of tumors. Normally, the ratio between the anabolic and catabolic

processes of a given tissue bears an orderly relation to that of all other tissues. In cancer, on the other hand, this relation is disturbed. Is this the result of a deficient control mechanism, or of evasion of this mechanism through novel avenues of synthesis? If such avenues exist, tracer methods may reveal them. Then chemotherapeutic methods may be found to block them.

In the metabolic process whereby energy is derived from carbohydrate, cancer tissue, in contrast with resting nonproliferating tissue, represents a shift toward the anaerobic. In other words, the economy tends to be glycolytic, as in a cell whose oxygen or respiratory system is inadequate.³¹ Warburg, the first to note this, ascribed it to a defect in the cancer cell.³² In recent studies by Salter, Burk and others, the respiration rate of normal tissue slices increased far more than that of tumor slices when a suitable substrate, such as succinic acid, was supplied; and thus the tumor tissue was shown to have the lower oxidative capacity, confirming Warburg's interpretation. One is reminded that Warburg, in his classic studies, went another step and attributed cancer to interference with the respiration of growing cells.³² But this is still an open question.

In recent studies by Hogeboom, Schneider and others, appropriate tests applied to cell fractions, isolated by centrifugation, demonstrated that essential respiratory enzymes, including cytochrome oxidase, are located on the mitochondria.³³

It is interesting that these cytoplasmic particles, the mitochondria, undergo pathogenic mutation in plants,³⁴ show morphologic changes in tumors,³⁵ and contain nucleic acid.³⁶

The following observations among others suggest a relation between nucleic acid and the origin and maintenance of cancer. All known duplicating units such as chromosomes, plastids and viruses contain ribose, deoxyribose or both kinds of nucleic acid in high concentrations; and ribose nucleic acid is high in certain cytoplasmic particles of virus size.³⁷ Moreover, studies such as those of Griffith and later Avery show that a nucleic acid is capable of invoking permanent cellular variations. In Griffith's experiment, one type of pneumococcus was transformed into another by contact with heat-killed organisms of the second type;³⁸ and Avery demonstrated that deoxyribose nucleic acid was the agent of the mutation.³⁹ Such observations suggest innumerable questions, of which a few may be raised in passing. What is the role of nucleic acid in the

synthesis of protein? What is its role in cytoplasmic particles such as microsomes and mitochondria? Is nucleic acid the active principle of a cancer virus? Does alteration of nucleic acid represent the long-sought 'common denominator' of carcinogenesis? Only further, intensive investigation can provide the answers.

The research attack upon cancer is launched on two main levels: the gaining of basic knowledge, with a long view toward practical application; and the search for improved methods of prevention, diagnosis and treatment in the absence of an adequate explanation of the cancer process. In facing the cancer problem, we are encouraged by the fact that in many diseases the cause was unknown at the time the fight was won. I should like now to discuss briefly research in cancer therapy.

For the past three years we have heard a great deal about the therapeutic use of radio-isotopes. The isotopes most thoroughly tested against various forms of human cancer have been radioactive phosphorus [P^{32}] and sodium [Na^{24}], for whole-body radiation, and radio-iodine [I^{131}] for cancer of the thyroid. In leukemia, treatment with radio-phosphorus has produced less radiation sickness than X-ray, but has not proved superior in prolonging life.⁴⁰

Before the radio-isotope can come into its own, means must be found for localizing these agents within the tumor, for the primary and metastatic cancer cells must receive many times as much radiation as the normal cells to warrant the treatment. Therapeutic doses must be administered with extreme caution. In several cases, such doses have been followed by aplastic anemia; and though insufficient time has passed to observe long-term effects, the dangers of radiation are well known. In clinical work involving localization of radio-isotopes in tumors, each treatment should be preceded by a small tracer dose, to determine whether adequate concentration in the tumor may be expected. Greater effort must be made to develop radioactive compounds with a high degree of tumor specificity. Until this is accomplished, the ultimate value of radio-isotopes in the treatment of cancer cannot be estimated.

During the late war, a class of compounds known as nitrogen mustards, which are closely related to mustard gas, were found to produce nuclear damage in cells. Subsequent investigation revealed that proliferating cells are most vulnerable.⁴¹ From clinical data obtained so far, the nitrogen mustards seem to deserve a place in the treatment of

Hodgkin's disease, polycythemia, lymphosarcoma, and perhaps some cases of chronic leukemia. In these conditions, temporary remissions of varying duration have been observed. But it must be emphasized that these agents are highly toxic, and insufficiently selective to be curative. Other compounds within this class are being synthesized and tested.

Urethan [ethyl carbamate], long known as a hypnotic, has been found effective in chronic myelogenous leukemia and, to a lesser degree, in similar conditions.⁴² In early cases, remissions lasting a few months may be obtained, but when the drug is discontinued, sudden relapse occurs. In advanced cases, this agent is inferior to radiation. I have mentioned that urethan induces pulmonary tumors in mice.

The compounds stilbamidine and pentamidine have been shown by Snapper and others to have some effect in multiple myeloma.⁴³ In conjunction with a low protein diet, these agents relieve pain and temporarily retard the disease. This is another indication that the cancerous cells most susceptible to damage are those of the blood or blood-forming organs.

In recent years a rational therapeutic principle has emerged from experiments with microorganisms—the principle of metabolite antagonism.⁴⁴ A *metabolite* may be regarded as a substance involved in the process of cellular growth and maintenance; an *antagonist*, a substance capable of interfering with the synthesis, utilization or function of a metabolite. An example of a metabolite is the vitamin folic acid; an antagonist to this, aminopterin. And under these definitions, one could include as metabolites the amino acids, enzymes and hormones. Several groups of compounds are being tested in laboratories and hospitals for possible antagonistic effect in the growth or maintenance of malignant cells.

In studies by Farber and others, folic acid antagonists have produced temporary remissions in a few children with acute leukemia.⁴⁵ At the National Cancer Institute, Law has obtained remissions in leukemic mice.⁴⁶ But these agents, too, are highly toxic, and are not recommended as yet for general use by the practitioner. Results to date, however, should encourage further investigation of these and other metabolite antagonists, especially in controlled experiments with animals. The underlying principle is sound and well worth pursuing.

I have mentioned the value of estrogen in the treatment of cancer of the prostate, and of androgen or estrogen in breast cancer. The

Therapeutic Trials Committee of the American Medical Association has undertaken the task of determining the optimal use of hormones in breast cancer therapy.⁴⁷ I shall not discuss the subject further, except to emphasize that to date hormonal treatment in cancer has been palliative only.

Another promising approach to the development of chemical agents for cancer therapy is the systematic screening of compounds known to damage cells. In this approach, it is initially recognized that the vulnerability of cancer tissue to an agent has always been shared by normal tissues. This is turned to advantage: known cytotoxic compounds are searched for those especially destructive to cancer cells; and as such agents are found, they are subjected to chemical modification designed to reduce toxicity or increase activity.

In a screening program under the direction of Shear at the National Cancer Institute, this is essentially the guiding principle in the selection of compounds for testing.⁴⁸ The workers represent a variety of scientific disciplines. Their concerted purpose is to find or develop chemical agents that either alone or combined with radiation or surgery will control tumors without prohibitive destruction of normal tissue.

Sarcoma 37 in the mouse is used in the preliminary screening of every compound. Transplanted tumors may be considered as artificially established, standardized metastases. Fifteen mice are used in the first testing of each agent.

So far, more than a thousand agents have been screened, and the results have far exceeded expectations. At a single dose near the lethal, definite tumor damage has been obtained in the last few years with about sixty compounds.⁴⁹

Although none of the sixty positive compounds completely destroys the test cancer, the results show decided progress, not only in providing agents for further study but in proving the value of a screening method in experimental cancer chemotherapy. We propose to continue the screening procedure. Moreover, the positive agents will be tested against several forms of cancer in various laboratory animals. On the basis of findings to date, the structures of effective compounds are being studied in terms of function, with a view to producing, through alteration of the original molecule, an agent safe for the host but fatal to the tumor.

This brief review of studies in cancer therapy does not purport to reflect the large amount of effort invested in this field. I have tried only

to indicate that there is such an effort, and to emphasize, to my deep regret, that no cure except surgery or radiation is as yet available. This is not to say, however, that highly encouraging results are lacking. In this difficult problem, we now appreciate that a concerted attack, based on sound scientific principles and following practical systematic lines of approach, is our best assurance of success. In laboratories and hospitals throughout the country, such an attack is under way.

Another approach that has yielded valuable information and is being intensified in cancer research programs is epidemiology. This term is used to designate investigation of the incidence of cancer by types and site with relation to total history including environment. This extension of the term 'epidemiology' is largely due to similarities of method to those used in the study of communicable disease. In cancer research, epidemiologic methods have contributed especially to our knowledge of causal factors in the environment of industrial workers.

Studies to identify environmental factors of carcinogenesis in industry and to develop means of controlling them usually proceed in four major steps. First, mortality rates by geographic region are searched for areas of high incidence. Second, the hazardous areas are searched for evidence of possible carcinogens, such as unusual industrial products. Third, the suspected agent is tested in the laboratory. If found carcinogenic, the fourth step is taken: measures are devised for protecting the workers and community. These steps, though not always applied in formal programs, have exposed a formidable host of carcinogenic agents and influences, including the following industrial materials: tar, shale oil, crude paraffin, creosote, crude anthracene, arsenic, benzol, chromates, asbestos, intermediates of aniline dyes, and the energy agents already mentioned.⁵⁰ At the National Cancer Institute, a program under the direction of Hueper has been established to detect other agents and to advise and assist industries in eliminating the hazards.

Another epidemiologic approach is to follow special population groups, in order to determine whether certain influences, such as a given diet or habit, will contribute to carcinogenesis. A familiar example of a habit that leads to cancer is the chewing of betel nut quids in Asiatic countries.⁵⁰ At present, strong clinical impressions indicate that groups with certain pathologic conditions, such as achlorhydria and pernicious anemia, should be traced with a view to deciding whether the incidence of cancer in these groups is higher than average. A major advantage of

such a program is the contribution to early case finding.

In coöperation with the University of Washington in Seattle, the National Cancer Institute is engaged in laboratory and clinical studies to develop a diagnostic test or tests for cancer. At present, tests reported in the literature are being evaluated through application to cancer patients and persons with other diseases. Coöperative arrangements have been established with local hospitals and physicians. Tests found effective on the advanced cancer patients in Seattle will be tried for mass-screening possibilities at the venereal disease clinic of the United States Public Health Service Medical Center in Hot Springs, Arkansas. The possibility that available material would yield a practical means of segregating persons for further examination should be thoroughly explored.

In this discussion I have not attempted to divide the subject matter by scientific disciplines, since cancer research, for the most part, is conducted on an 'interdisciplinary' basis. This tendency to transcend departmental barriers represents an important advance. In the past, outstanding contributions were made in isolated fields, such as pathology, physics and surgery, to which must be credited, respectively, microscopic examination of tissue, which remains the most reliable method of cancer diagnosis, and radiology and radical excision, the only cures. Now that a groundwork has been laid, however, those disciplines are drawn upon by others, which build in turn an indispensable foundation.

A voice from antiquity bespoke the interdisciplinary approach: Bacon said: "The strength of all sciences, which consists in their harmony, each supporting the other, is as the strength of the old man's fagot in the band; for were it not better to set up one great light, or branching candlestick of lights, than to go about with a small watch candle into every corner?" James Ewing was among the first to conceive of a cancer institute in the modern sense—as an institution where scientists of many disciplines combine their efforts and resources in a common mission, cancer research. In the future an even closer integration of disciplines must be achieved.

Integration of laboratory and clinical investigation in cancer is requisite throughout the country. At the National Institutes of Health, this need will be met with the completion of the new Clinical Center, in which 100 beds will be used for cancer patients. Ground is now being prepared for the buildings, which are expected to be completed in about

two years. The Center will make possible direct application of basic findings, and will help meet the national need for clinical cancer studies.

This general view of cancer research may warrant a general conclusion. From the facts gleaned in recent years, through much profound thought and unremitting toil in laboratories and clinics throughout the world, one may deduce that cancer, contrary to the word of some discouraged early workers, is not an unsolvable mystery of the universe. It is a practical scientific problem, and science in its stride can conquer it. But the problem, I repeat, is subtle; the solution may not come soon; and the attack, at least for the present, must include much basic investigation and must advance on a broad front.

I should like to close on a note of caution. The people of the world have a vital stake in the progress of cancer research, and are entitled to full and fair reports of scientific accomplishment. Because of the great eagerness of the public for news that cancer research is 'on the right track,' that the long-sought cure is at hand or close to it, reports of moderate advances are frequently exaggerated. Because the wish is father to the thought, hopeful new leads may be mistaken for fully developed answers to major questions.

The penalty of exaggeration is disillusionment. Our outlook in cancer research is optimistic; all of us hope that the solutions to the problems are not too far off, and there is no reason to believe that they are. But the available evidence does not necessarily indicate that the solutions are right around the corner. The distance ahead, as well as a balanced interpretation of achievements, must be emphasized in every progress report.

A concerted attack on cancer is being made today through the efforts of universities, general and cancer hospitals, voluntary organizations such as the American Cancer Society, and of Federal agencies such as the National Cancer Institute and the Atomic Energy Commission. Through continued support of these efforts as long as necessary, by a generous and confident nation, the cancer problem will be solved.

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AN EVALUATION OF THE SURGICAL
TREATMENT OF HYPERTENSION*

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I

In a discussion of the surgical treatment of hypertension, three procedures should be mentioned, unilateral nephrectomy, the removal of adrenal tumors, and sympathectomy.

Unilateral Nephrectomy: The percentage of hypertensive patients who have a unilateral renal lesion which would justify nephrectomy is very small, probably a fraction of one per cent. The statistical chance that removing such a kidney will favorably influence the course of the disorder is in the vicinity of 20 per cent according to Smith¹. It would seem reasonable to use the same indications for nephrectomy in hypertensive patients as in non-hypertensive patients.

Adrenal Tumors: It is difficult to estimate the incidence of adrenal tumors among hypertensive patients. In those cases I have treated surgically in whom the adrenal glands were carefully inspected and palpated, the incidence was approximately 5 per cent. One tumor in ten proved to be a pheochromocytoma, an incidence of 0.5 per cent. The vast majority of the remaining tumors were cortical adenomas and with one exception did not appear to influence the hypertension materially. It is therefore apparent that adrenal tumors together with the even rarer paragangliomas are factors of importance in less than 1 per cent of hypertensive patients. Because the result of removing these tumors is almost always worthwhile, it is important that the diagnosis be made. In this connection it should be reëmphasized that although many pheochromocytomas cause paroxysmal attacks of hypertension, others produce a continued non-paroxysmal form of the disorder. To differentiate the latter group from patients having so-called essential or

* Presented October 7, 1948 before the 21st Graduate Fortnight of The New York Academy of Medicine.

malignant hypertension may be difficult. Most of our patients have fallen into the latter category, and the tumors were discovered only because the adrenal glands were explored. Certain signs and symptoms which in retrospect would appear to be of diagnostic value have been noted. Among these are excessive sweating, postural hypotension with tachycardia, normal cold pressor response, hypermetabolism, altered peripheral blood flow, hyperthermia, and hyperglycemia. This small but interesting group of patients will be discussed in greater detail in the near future.

OPERATIONS UPON THE SYMPATHETIC NERVOUS SYSTEM

In by far the largest number of hypertensive patients who have been treated surgically, a sympathectomy of one sort or another has been performed. The first attempt to modify the course of hypertensive cardiovascular disease by sympathectomy was made in 1924. Numerous reports have appeared in the literature since that time.²⁻¹⁰ The first operation was a periarterial sympathectomy upon the left femoral artery of a young male suffering from the most severe form of the disorder, so-called malignant hypertension, in its terminal stage. This operation was performed by Adson. In the following year he operated upon a second patient, this time performing a bilateral lumbar sympathectomy. Their experiences with these two patients were discussed by Rowntree and Adson in 1925.¹¹

As time has gone on, operations upon the sympathetic nervous system have become more and more extensive. Every conceivable variation has now been tried, including total sympathectomy in a few cases. I would estimate that at least 5,000 and possibly 10,000 hypertensive patients have been treated by one form of sympathectomy or another in this country during the past twenty years. At the same time, probably hundreds of thousands of patients have been treated in other ways. One might therefore think that it would be possible to evaluate one form of therapy or another with finality at this time. This, however, is not the case.

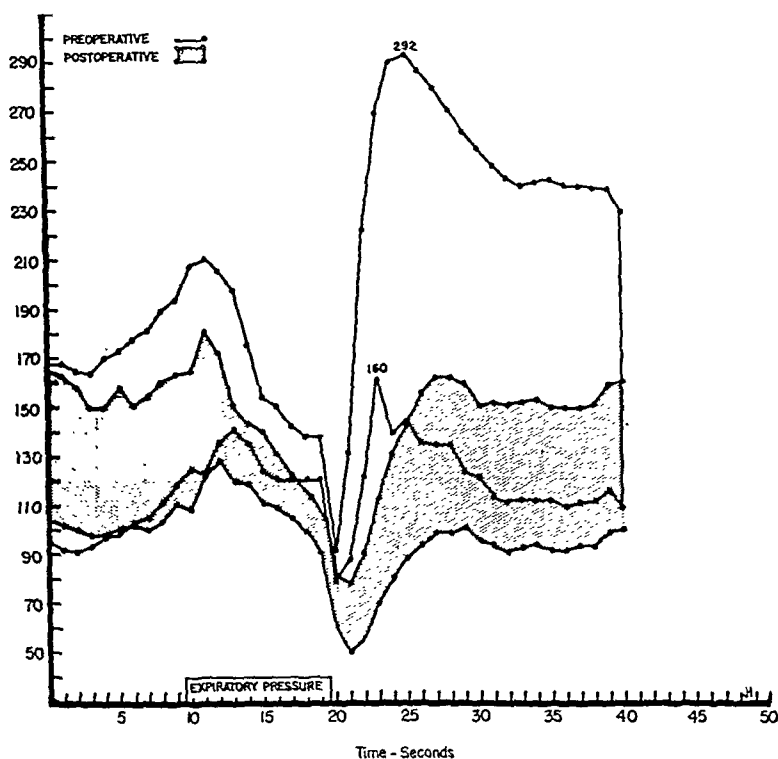
EVALUATION OF SPLANCHNICECTOMY—PHYSIOLOGIC EFFECTS

In evaluating a therapeutic measure, consideration must be given to the nature of its effect upon the disorder in question. Any therapeutic value which sympathectomy may have is undoubtedly due

to the physiologic effects of this procedure upon the cardiovascular system. These fall into two categories,—known and presumed. Of the known effects there are two,—modification of blood pressure levels and modification of the reflex regulation of blood pressure resulting from the inactivation of important components of the vasoconstrictor mechanism. Of the presumed effects, abolition of reflex secretion of adrenin and stabilization of blood flow through the denervated vascular bed might be mentioned.

Effect of Splanchnicectomy Upon Blood Pressure Levels: Reduction in blood pressure levels varying from slight to marked, lasting from one to ten years, have followed the denervation of large vascular areas. The percentage of patients in whom significant changes in blood pressure levels have been noted varies in the different series from about 20 per cent to as high as 75 per cent. The percentage will vary because the criteria used for judging changes in blood pressure differ and because there are wide variations in the patient material and operative techniques in the different series. It has been difficult to predict just what the effect of operation upon blood pressure levels will be in unselected cases and how long it will last. Judging from my own experiences, 66 per cent of unselected patients with persistently elevated blood pressure with associated cardiovascular changes have had a slight to marked reduction in blood pressure lasting from one to five years.¹² In the five to ten-year follow-up period, 47 per cent of these same patients have had a blood pressure reduction comparable to that noted during the first five-year period.¹³ This indicates a definite tendency for blood pressure to return to or towards preoperative levels with the passage of time. The great majority of patients who have had prolonged and persistent reductions in blood pressure levels have done well as judged by mortality rates and improvement in or lack of progression of cardiovascular disease. In occasional instances, cardiovascular disease has progressed in spite of marked and persistent reduction in blood pressure levels. In other cases, improvement in the status of the cardiovascular system has been noted in the absence of any demonstrable change in blood pressure levels. The favorable effect of sympathectomy does not appear to be solely dependent upon the lowering of blood pressure levels.

Effect of Splanchnicectomy Upon Reflex Control of Blood Pressure: The second known physiologic effect of splanchnicectomy is a marked alteration in the reflex control of blood pressure. This has been recently



* Fig. 1—Response to Valsalva test before and after lumbo-dorsal splanchnicectomy. Variations in blood pressure caused by reflex vasoconstriction are abolished when a large vascular area such as the splanchnic bed is denervated. These variations may be very marked, as in this case. This physiological effect of sympathectomy occurs regardless of whether the basal levels are altered or not and is well demonstrated by the Valsalva maneuver as in this figure. Intra-arterial blood-pressure levels are optically recorded with a Hamilton manometer before, during, and after a ten-second period of forced expiration. Before operation there was a sharp overshoot of blood pressure to very high levels within a few seconds after the expiratory period. After operation (shaded graph) the overshoot was abolished. It seems probable that the elimination of such reflex variations in blood pressure is partly responsible for the favorable changes in the cardiovascular system which may be noted after operation.

demonstrated by Wilkins et al.¹⁴ In response to various stimuli, blood pressure levels may rise abruptly to high levels in normally innervated patients. This may be a factor of considerable importance in connection with the rate of progress of cardiovascular disease. These sudden elevations of blood pressure occur within a few seconds following stimulation. These are readily demonstrated by the Valsalva maneuver, during

* Reproduced from the British Medical Journal, 2: 237, 1948.

which intraarterial blood pressure levels are optically recorded by means of the Hamilton manometer. These reflex variations in blood pressure are almost always completely abolished following the denervation of a large vascular area. This effect occurs irrespective of changes in basal blood pressure levels and is well demonstrated by Figure 1. The effect has been shown to persist for years after operation, even in patients in whom the blood pressure has returned to or near preoperative levels. It is reasonable to believe that the prolonged abolition of marked overshoots in blood pressure due to reflex vasoconstriction would reduce the stress and strain upon the cardiovascular system.

Untoward Physiologic Effects: Among the physiologic effects of operation which are troublesome to the patients are postural hypotension with tachycardia, increased perspiration and coldness in the undenervated areas. The magnitude and duration of postural hypotension varies with the extent of the operation into the lumbar areas. Unless postural hypertension without unusual tachycardia is present before operation, it is our routine to remove the sympathetic trunks bilaterally from the eighth thoracic to the first lumbar segments inclusive. The postural hypotension after such a procedure is generally not particularly troublesome and is readily counteracted by bandages and girdles. These are usually discarded in about three months. More extensive denervations result in more prolonged postural effects. It has not been demonstrated as yet that they are indicated as a routine measure. It is most important to avoid lumbodorsal splanchnicectomy in hypertensive patients with unusually rapid heart rates. In these, postural hypotension and tachycardia may be very troublesome and disabling. A thoracic sympathectomy including the cardiac innervation but preserving the lumbar outflow is indicated in such cases. If care is taken to adjust the operative procedure to the patient, prolonged disability can be avoided without sacrificing therapeutic effectiveness. If loss of ejaculation is important, the lumbar ganglia should be preserved on one side. Increased perspiration in undenervated areas in hot weather and vasoconstriction in cold weather are unpleasant but not serious sequelae. The symptoms which are acquired as a result of the operation are usually more than counterbalanced by the improvement in symptoms present prior to operation. Of the patients who have been reexamined 5 to 10 years after operation, 83 per cent state that the favorable effects of operation definitely outweigh the unfavorable effects. Improvement in or relief

of headaches was obtained by 92 per cent of cases. Headaches of consequence were not present in 27 per cent of cases prior to operation. Most patients return to work in the course of three to six months. This, together with the hospital stay and its associated expense, introduces an economic factor which must be considered. If on the other hand, the patient's useful life expectancy is materially increased, this factor is more than counterbalanced. It seems proper to caution against too extensive operative procedures and to emphasize the need for selecting the proper type of denervation for the individual patient. If the operation is either too extensive or inappropriate, the untoward effects will frequently outweigh the beneficial effects.

Operative Mortality and Morbidity: The operative mortality has been low considering the advanced cardiovascular changes which have been present in many patients. The operative mortality and morbidity vary with the surgical technique employed. The transthoracic approach carries the highest mortality and morbidity. In experienced hands and with careful attention to preoperative preparation, anesthesia, and postoperative care, the operative mortality should be in the vicinity of 1 per cent. Of utmost importance is the replacement of operative and postoperative blood loss. In virtually every patient it should be presumed that slow, insidious oozing will take place into the operative field during the early postoperative period. This frequently will amount to 500 cc. or more and exceeds operative blood loss in importance. This can be detected by hematocrit determinations on the third and sixth postoperative days. In all cases, particularly in those with more advanced cardiovascular disease, it is essential that blood loss be replaced and hematocrit levels be maintained.¹⁵ This will significantly reduce operative mortality and morbidity.

As a rule, the operative procedures are carried out in two stages about ten days apart. For the lumbodorsal technique, the average hospital stay is thirty days. Transthoracic procedures are utilized by us in cases in which we wish to include the heart in the denervated area. This technique is employed in hypertensive patients having coronary heart disease with angina pectoris or in patients with tachycardia. The operations are performed two weeks apart and the total hospital stay is usually lengthened by a week or so. This technique is employed in about 20 per cent of patients and the lumbodorsal extrapleural technique in about 80 per cent. The principal source of postoperative discomfort

TABLE I

Vascular Area	No. of Cases	Status 5-10 Years After Lumbo-dorsal Splanchnicectomy		
		Improved	No Change	Worse
Retinal	120	41%	39%	20%
Cardiac	125	42%	49%	9%
Renal	114	29%	61%	10%
All (including cerebral)	100	51%	12%	37%

is intercostal neuritis. This can be greatly minimized by reducing operative trauma.

Effect of Sympathectomy Upon Cardiovascular Disease: Following sympathectomy, attention has been called to favorable changes which have been noted in the cardiovascular system. Most reports are concerned with patients followed for a few months to a few years. To date only two publications have dealt with more than small numbers of surgically treated patients followed for five years or more. The first was by Peet and Isberg,¹⁶ and the second, a recent report by this author.¹³ A follow-up period of at least five years seems necessary in order to begin to evaluate the effect of operation upon the cardiovascular system and to study the rate of progress of cardiovascular disease. It may be necessary to follow patients for ten or more years to evaluate this aspect of the problem accurately. Peet and Isberg reported improvement in the eyegrounds of 62 per cent of 146 patients followed for five to eleven years. Unfavorable changes were noted in 3 per cent of the cases. The remaining 35 per cent showed no change. They noted that during a similar follow-up period, 91 per cent of 80 hearts which were normal in size before operation did not change significantly, while 9 per cent became larger. Of 48 enlarged hearts, 52 per cent decreased in size, 44 per cent remained the same, and 4 per cent enlarged. Of 84 cases with normal electrocardiograms, 93 per cent showed no change and 7 per cent became worse. Of 57 abnormal electrocardiograms, 53 per cent improved, 42 per cent were unchanged, and 5 per cent were worse. Of 62 patients having normal renal function prior to operation, there was no change in 82 per cent and a reduction in 18 per cent. Of 55

TABLE II—ELECTROCARDIOGRAMS OF NON-SURGICALLY AND SURGICALLY TREATED HYPERTENSIVE PATIENTS FOLLOWED FOR 5 YEARS OR MORE

Author	Treatment	No. Cases	Improved	No Change	Worse
Canabal, Thomson, and White, P.D. (1945)	Non-Surgical	50	10%	40%	50%
Rasmussen and Boe (1945)	Non-Surgical	39	8%	56%	36%
Isberg and Peet (1948)	Surgical	184	19%	76%	5%
Smithwick (1948)	Surgical	125	42%	49%	9%

cases with impaired function, 36 per cent were improved, 53 per cent unchanged and 11 per cent were worse. The status of the various vascular areas of the first 100 or more cases to be followed for 5 to 10 years after lumbodorsal splanchnicectomy are summarized in Table I.

The significance of these data depends upon a comparison with similar data concerning non-surgically treated hypertensive patients followed for comparable periods of time. Unfortunately very little comparable data are available at this time. I have been able to find some information concerning the status of the electrocardiograms of hypertensive patients who were not treated surgically and who were followed for five years or more in the reports of Canabal, Thomson, and White¹⁷ and of Rasmussen and Boe.¹⁸ These are summarized in Table II and are compared with the most recent findings of Isberg and Peet¹⁹ and with those which I have reported. The comparison is very much in favor of the surgical series, is very significant statistically, and suggests that the course of hypertensive heart disease as judged by the electrocardiograms has been favorably modified by surgical treatment. In Table II the statistics of four authors are compared without regard to the original status of the electrocardiograms, since these data were not available for the patients who were not treated surgically. Of the 184 cases in the Isberg and Peet series, the electrocardiograms were normal in 101 and abnormal in 83 cases before operation. There was no change in 94 per cent and an unfavorable change in 6 per cent of the normal group during the five to twelve-year period following operation. Improvement was noted in 41 per cent of the abnormal group, with no

change in 55.4 per cent and an unfavorable change in 3.6 per cent. Of the 125 cases in my series, 55 had normal and 70 abnormal electrocardiograms before operation. In the normal group, there was improvement in 14.5 per cent, no change in 80 per cent and an unfavorable change in 5.5 per cent. In the abnormal group there was improvement in 64.3 per cent, no change in 24.3 per cent and an unfavorable change in 11.4 per cent. The time of follow-up was five to ten years for the 125 cases. We have used the criteria of Canabal, Thomson and White in evaluating changes in the electrocardiograms. Because there is considerable variation in the normal range, it is possible for an electrocardiogram, originally normal, to improve.

Much more data concerning the progress of cardiovascular disease in our surgically treated patients will become available as the follow-up progresses. It is important that the data which are available concerning patients who have not been treated surgically be supplemented as soon as possible. In this connection, the following quotation from the article of Canabal, Thomson and White is pertinent. "Having become interested in these electrocardiographic changes following splanchnic sympathectomy, we sought in vain for published reports of comparable and adequate control studies, that is, studies of the evolution of the hypertensive electrocardiogram in patients without such operation. Hence, we have collected as many such data as we have as yet been able to find which were based on adequate criteria. This search has been difficult and has yielded only fifty cases."

MORTALITY AMONG HYPERTENSIVE PATIENTS

An evaluation of the surgical treatment of hypertension should take into consideration the effect of the procedure upon the mortality rate. In the final evaluation of any therapeutic measure, its effect upon life expectancy will be the most important consideration. The mortality rates for hypertensive patients followed for four to eleven years who were not treated surgically may be judged from representative reports in the literature. Those of Janeway,²⁰ Blackford, Bowers, and Baker,²¹ Keith, Wagener and Barker,²² Rasmussen and Boe,¹⁸ and Bechgaard²³ are summarized in Table III. The mortality rates vary widely in the different series, from 28 per cent to 91 per cent. Obviously, there must have been a considerable difference in the patient material comprising the various series. In the majority, the mortality was high. It becomes

TABLE III—MORTALITY AMONG HYPERTENSIVE PATIENTS
NOT TREATED SURGICALLY

<i>Author</i>	<i>No. Cases</i>	<i>Time Followed</i>	<i>Mortality</i>
Janeway (1913)	458	1-10 years	50%—5 years 75%—10 years
Blackford, Bowers, and Baker (1930)	202	5-11 years	50%
Keith, Wagener, and Barker (1939)	219	5-9 years	91%
Rasmussen and Boe (1945).....	100	6 years	52%
Bechgaard (1946)	1,038	4-11 years	28%

TABLE IV—MORTALITY AMONG HYPERTENSIVE PATIENTS
NOT TREATED SURGICALLY

<i>Author</i>	<i>Males</i>	<i>Females</i>
Janeway (1913)	53%	33%
Blackford, Bowers and Baker (1930).....	70%	39%
Keith, Wagener, and Barker (1939).....	93%	88%
Rasmussen and Boe (1945).....	71%	43%
Bechgaard (1946)	41%	22%
Average.....	66%	45%

apparent that it is impossible to compare mortality rates for different groups of hypertensive patients unless they are divided into subgroups in which some of the important variable factors present in this disorder are held constant. Before mortality rates can be used as a measure of the value of any particular form of therapy, this must also be done. The more variables that can be controlled, the more accurate will be the conclusions. Among the many important variables are the sex of the patient, the severity of the hypertension as judged by the resting diastolic blood pressure level and the grade of eyeground change. The age factor should also be taken into consideration. About 90 per cent of the patients in my series are below 50 years of age. The majority of patients in non-surgically treated series are over 50 years of age.

TABLE V—MORTALITY AMONG HYPERTENSIVE PATIENTS TREATED SURGICALLY

Author	Technique	No. Cases	Time Followed	Total	Mortality	
					Males	Females
Peet and Isberg (1946)	Supradiaphragmatic Splanchnicectomy	437	5-12 years	42.5%	62%	30%
Smithwick (1948)	Lumbodorsal (thoracolumbar) Splanchnicectomy	317	5-10 years	29%	35%	25%

Influence of Sex Upon Mortality: The importance of the sex factor is clearly brought out by Table IV, in which the mortality rates for the male and female patients of the same authors quoted in Table III are given. It is very apparent that the mortality among males is much higher than among females, the average rate for the former being 66 per cent and for the latter 45 per cent during a comparable period of observation. It is therefore clear that in evaluating therapy, the sex factor must be taken into consideration.

The mortality rates for surgically treated patients followed from five to ten years or more are summarized in Table V. With regard to my statistics, it should be stated that during the first 5 years of the study, from October, 1938 through September, 1943, a total of 330 patients with continued hypertension and cardiovascular changes varying from slight to marked were operated upon. A bilateral lumbodorsal splanchnicectomy was performed in all of these cases. As of September 1, 1948, thirteen of the patients are untraced. This represents 4 per cent of the total material. The remaining 317 cases were operated upon at least five and at most ten years ago. Of these, 225 are living and 92 are dead, a mortality of 29 per cent. The mortality for males was 35 per cent and for females 25 per cent, again emphasizing the higher death rate among males. The difference in the mortality rate for the two sexes, however, was not nearly as great as in those cases who were not treated by lumbodorsal splanchnicectomy. These statistics are included in Table V, which also contains comparable data from the Peet and Isberg series. The over-all mortality differs in the two series, that for male patients being much lower in the lumbodorsal series. The

TABLE VI—MORTALITY AMONG HYPERTENSIVE PATIENTS
Six Years after First Examination or 5 to 10 Years after Operation

<i>Resting Diastolic Level</i>	<i>Rasmussen and Boe</i>			<i>Smithwick</i>		
	<i>No. Cases</i>	<i>No. Deaths</i>	<i>Mortality</i>	<i>No. Cases</i>	<i>No. Deaths</i>	<i>Mortality</i>
90-109 ———	46	20	43%	80	5	6%
110-124 ———	31	18	58%	98	24	25%
125+ ———	19	14	74%	139	63	45%

mortality rates for both males and females are considerably lower in the lumbodorsal series than the average for the cases not treated surgically.

Mortality According to Resting Blood Pressure Level: The blood pressure level of a particular hypertensive patient is difficult to evaluate. There is no generally accepted method for determining this figure. Many authors utilize ambulatory blood pressure data. Because of the fact that ambulatory pressures may be elevated and resting pressures much lower or within the normal range we have felt that it was preferable to use resting levels. There is no unanimity of opinion as to what constitutes a resting level. Some authors feel that a rest period of many days or even weeks is desirable. Our plan has been to have the patients rest for forty-eight hours in order to detect patients with transient or intermittent hypertension. Patients with diastolic levels below 90 resting and over this figure when active are classified as having transient or intermittent hypertension. We have operated upon a few such cases and they will be reported separately. Patients with resting diastolic levels of 90 m.m. or more are regarded as having persistent hypertension. This report deals with such cases. While it is undoubtedly true that the diastolic levels of some cases would fall to lower levels with a longer rest period, we have felt that rest beyond a certain point becomes a therapeutic measure and for practical purposes is not as satisfactory as a short rest period for differentiating between transient and persistent hypertension. Prolonged bed rest would, however, differentiate between varying degrees of persistence of hypertension.

Rasmussen and Boe¹⁸ hospitalized their patients and divided them into three groups on the basis of resting blood pressure levels. The levels

TABLE VII—MORTALITY AMONG HYPERTENSIVE PATIENTS
5-10 Years After First Examination or Operation

<i>Hypertension Group or Grade Eyegrounds</i>	<i>Keith, Wagener, Barker</i>			<i>Smithwick</i>		
	<i>No. Cases</i>	<i>No. Deaths</i>	<i>Mortality</i>	<i>No. Cases</i>	<i>No. Deaths</i>	<i>Mortality</i>
1 ———	10	4	40.0%	86	9	10.5%
2 ———	26	17	65.3%	89	22	24.8%
3 ———	37	34	92.0%	82	37	45.2%
4 ———	146	145	99.3%	42	22	52.4%

selected were 90-109, 110-124, 125 and over. The mortality rates for cases falling into the three groups were determined after a period of six years had elapsed since the original examination. We have divided our 317 cases in the same fashion and the mortality rates are included for comparison in Table VI. In their series, as in ours, the mortality rate increased as the resting diastolic level increased. The rates were considerably lower in the corresponding groups treated surgically.

Mortality According to Eyeground Changes: In 1939, Keith, Wagener and Barker²² emphasized the importance of the changes in the eyegrounds of hypertensive patients as a guide to prognosis. A series of 219 patients was divided into four groups largely on this basis. The patients who fell into group I had mild narrowing or sclerosis of the retinal arteries. Those in group II had moderate to marked sclerosis of the retinal arteries characterized especially by exaggeration of the arterial reflex and arteriovenous compression. Group III contained patients with angiospastic retinitis characterized especially by edema, cotton-wool exudate and hemorrhages in the retina superimposed upon a combination of sclerotic and spastic lesions in the arterioles. If measurable edema of the optic discs was added to this picture the case was placed in group IV. These patients were followed for a period of five to ten years at which time the mortality rates were determined and survival curves were constructed for each of the four groups. The prognosis was shown to vary for each group. They felt that their series of cases offered a good control for any specific form of therapy since treatment consisted of general measures, especially with regard to diet and rest and the regular use of certain sedatives.

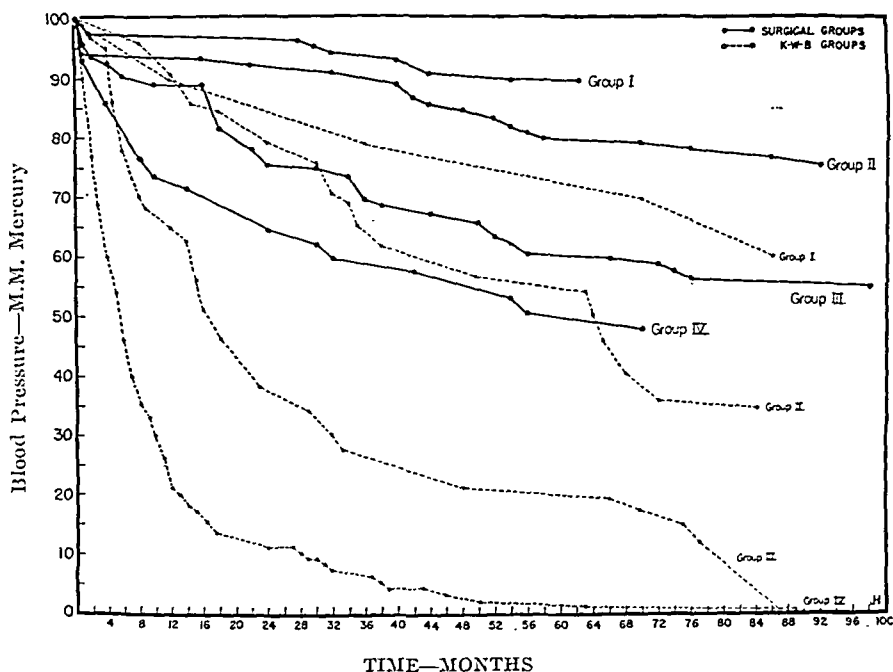


Fig. 2—In this figure the survival curves for 299 hypertensive patients treated surgically are compared with the survival curves for the Keith, Wagener and Barker series of 219 medically treated patients. Both series are divided into four groups according to Keith, Wagener and Barker criteria. The survival curves for the surgical series (heavy lines) may be compared with those of the medical series (dotted lines) group for group. It is apparent that the survival rate is much higher in the surgical series group for group. The number of patients in the medical series group 1 is too small for statistical analysis. The difference in the survival rates for medical and surgical patients in groups 2, 3 and 4 is highly significant statistically. This indicates that the life expectancy for these patients has been materially increased by surgical therapy.

Because of their observations, we have arranged our cases into four groups using their eyeground classification as the primary basis for this subdivision. Of the 317 cases in our series, 18 were considered to have normal eyegrounds. Since there were no cases of this sort in the Keith, Wagener and Barker series, we have eliminated these. The remaining 299 cases have been divided into four groups. The mortality rates for the five to ten-year period after operation are given in Table VII. The findings of Keith, Wagener and Barker are included for comparison. The mortality rates for the different groups vary in our series just as in theirs. There is, however, a marked difference between the cor-

TABLE VIII—METHOD USED FOR DETERMINING THE NUMERICAL GRADE OF HYPERTENSIVE PATIENTS

<i>Factors To Be Considered</i>		<i>Numerical Value of Each Factor</i>
C.V.A. without or with minor Residual Abnormal ECG Enlarged Heart Impending Failure	P.S.P. less than 25% in 15 minutes or 60% in 2 hours Age 50 or over Mild Angina	1
C.V.A. with Residual* Frank Congestive Failure Moderate Angina	P.S.P. less than 20% in 15 minutes Unsatisfactory response to sedation	2
P.S.P. less than 15% in 15 minutes		3
Nitrogen Retention		4

* Cerebral deterioration or definite involvement of arm and/or leg.

responding groups in the two series in favor of the patients who were treated surgically. There are too few group I cases in the control series for statistical analysis. The differences observed between group II, III, and IV cases are highly significant statistically. This indicates that the prognosis for many hypertensive patients has been significantly improved by surgical therapy. The same data, presented in the form of survival curves, are shown in Figure 2. This is a figure comparing 299 surgical cases with Keith, Wagener and Barker's 219 medical cases.

SELECTION OF CASES FOR SPLANCHNICECTOMY

Since this paper was presented, further control data for non-surgically treated patients have appeared in the literature. Palmer, Loofbourow and Doering²⁴ have given mortality rates for 430 cases treated medically and followed for an average period of 8 years. These cases were divided into four groups according to the severity of the cardiovascular changes at the beginning of treatment. Their classification differs from that of Keith, Wagener and Barker in that the degree of damage in the most affected area is the determining factor for grading, rather than the change noted in the eyegrounds. This classification is also helpful in arranging patients into more comparable groups but as

TABLE IX—TWO EXAMPLES OF THE METHOD FOR DETERMINING THE NUMERICAL GRADE OF HYPERTENSIVE PATIENTS

EXAMPLE 1		EXAMPLE 2	
Factors Considered	Numerical Value	Factors Considered	Numerical Value
Abnormal ECG _____	1	Abnormal ECG _____	1
C.V.A. without residual _____	1	Enlarged Heart _____	1
P.S.P. 20% in 15 minutes _____	1	P.S.P. 10% in 15 minutes _____	3
Total _____	3 = Numerical Grade	Total _____	5 = Numerical Grade

with the Keith, Wagener and Barker classification still permits of wide variations in the patient material in each group because so many other variables of importance are not controlled.

For this reason we have adopted a method for grouping hypertensive patients in which many variable factors are controlled. In order to decide into which of our five groups a particular patient belongs, it is first necessary to determine the numerical grade of the patient. For this purpose, many of the variable factors which have been discussed are assigned a numerical value. This plan is somewhat similar to that utilized by Hinton.¹⁰ The numerical value for each of the factors considered is given in Table VIII. The total of the numerical values determines the numerical grade of a particular patient. Two examples of this plan for estimating the numerical grade are given in Table IX.

It was found that the mortality rate over a five to ten-year period of observation following operation was 12 per cent for patients with a numerical grade of less than 4, and 62 per cent for those with numerical grade of 4 or more. Consequently the cases were divided into two groups according to whether the numerical grade was less than 4 or 4 or more. Patients with a numerical grade of less than four will fall into our groups 1 or 2. Those with a numerical grade of 4 or more will fall into our groups 3, 4 or 5. The other factors which determine the group for a particular case, in addition to the numerical grade, are the sex, eyegrounds, the severity of the cardiovascular changes in the cerebral, cardiac or renal areas, and the severity of the resting diastolic blood

TABLE X—CLASSIFICATION OF HYPERTENSIVE PATIENTS
Criteria for Grouping

<i>Group</i>	<i>Numerical Grade</i>	<i>Other Factors</i>
1	Less than 4	Females and males, eyegrounds grade 0 or 1. Females with eyegrounds grade 2 or 4.
2	Less than 4	Females with eyegrounds grade 3. Males with eyegrounds grade 2, 3, or 4.
3	4 or more	Resting diastolic level below 140 m.m. C.V.A. with residual, or frank congestive failure, or a P.S.P. below 15% in 15 minutes combined with a poor response to sedation, not present.
4	4 or more	Same as 3 except one or more of cardiovascular changes referred to are present.
5	4 or more	Resting diastolic level 140 m.m. or more.

pressure level. These are indicated by Table X. It is thus possible to place any hypertensive patient into one of our five groups and since so many variables are controlled, it should make the patient material in each group much more comparable. It should be understood that this discussion applies only to patients who have persistent hypertension as we have defined it, and does not apply to patients with so-called transient hypertension.

In Table XI, the observed mortality rates for the patients in each of our five groups are given. The estimated mortality rates for these same patients as judged by both the Keith, Wagener and Barker, and the Palmer, Loofbourow and Doering control data are also recorded for comparison. It is apparent that there is a very marked difference for group 1, 2 and 3 patients, but no difference for group 4 and 5 patients. This indicates that surgery has failed to modify the mortality rate for patients in groups 4 and 5; and I feel that this constitutes adequate reason for advising against operation in patients who fall into these two groups. On the other hand, it appears that operation has been well worthwhile for patients falling into our groups 1, 2 and 3. A more detailed discussion of this matter is in press.²⁵

SUMMARY

The surgical treatment of hypertension is discussed with particular reference to operations upon the sympathetic nervous system.

TABLE XI—MORTALITY RATES FOR SURGICALLY TREATED HYPERTENSIVE PATIENTS FOLLOWED 5-10 YEARS COMPARED WITH MORTALITY RATES ESTIMATED FROM THE KEITH, WAGENER AND BARKER, AND PALMER, LOOFBOUROW AND DOERING CONTROL DATA

Surgical Series (Smithwick)				Medical Series	
Observed Mortality				Mortality Estimated From	
Group	No. Cases	No. Deaths	Mortality	K.W.B. Data	P.L.D. Data
1	175	13	7%	54%	47%
2	80	18	23%	86%	84%
3	52	14	27%	73%	74%
4	38	31	82%	79%	82%
5	36	33	92%	91%	83%

The favorable as well as the unfavorable effects of surgery of this type are commented upon. If too radical and inappropriate procedures are avoided, the beneficial effects will outweigh the untoward effects in the great majority of cases.

Such comparisons as can be made between surgically and non-surgically treated hypertensive patients followed for five to ten years are distinctly favorable to the surgical series.

The necessity for dividing hypertensive patients into more comparable groups, in which many of the variable factors encountered in this disorder are controlled, is emphasized.

A plan for dividing hypertensive patients into five groups is presented. The actual and estimated mortality rate for each group is given. On this basis, it appears that surgery has been well worthwhile in group 1, 2, and 3 cases. It has not affected the prognosis in group 4 and 5 cases and appears contraindicated in patients falling into these two groups.

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RECENT ADVANCES IN THE THERAPY OF THE MORE COMMON PROTOZOAN AND HELMINTHIC INFECTIONS OF MAN*

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INTRODUCTION

I AM DISCUSSING recent advances in the treatment of parasitic infections, one must not overlook the fact that specific agents for the therapy of some of these infections antedate by centuries so called modern chemotherapy. The story of quinine is well known and needs no comment. Male fern was known to Pliny and Galen, and was used extensively in Europe in the 18th century against tapeworms. The essential oils were used as anthelmintics by the American Indians in the days of Columbus, and specifically against hookworm in Europe in 1881. Screening techniques now used in the search for therapeutic agents against infections were first systematically explored in the experimental chemotherapy of parasitic diseases. As a result important contributions were made in the treatment of animal and human parasitic infections. In addition, the extension and application of some of these agents in the treatment of non-parasitic diseases have given us in more recent times extremely useful drugs, of which salvarsan and the sulfonamides are perhaps the most notable examples.

During the recent war we had to maintain our men in good health in tropical areas in spite of potentially great risks of infection and morbidity from parasitic infections. This necessitated re-evaluation of existing therapeutic agents as well as stimulated the systematic search for new, possibly more efficient drugs and better schedules of treatment.

In my discussion tonight I will review the present status of the therapy of such parasitic infections which ordinarily occur in this country, or, which by virtue of their introduction in a significant number of veterans, may constitute a small segment of the patient population.

* Presented at the Graduate Fortnight, The New York Academy of Medicine, October 15, 1948.

INFECTIONS CAUSED BY PATHOGENIC PROTOZOA

From the standpoint of total numbers, potential disability, or the likelihood of their occurrence in medical practice in the United States, the infections caused by the plasmodia and *Endamoeba histolytica* are the most important ones produced by protozoa. Consequently discussion of the latter will be limited to the treatment of malaria and amebiasis.

MALARIA

This disease occurs normally in the United States, and in addition one should note that more than a half million hospital admissions during World War II were attributable to malaria. The progress in the treatment of this infection will be reviewed briefly by consideration of the following: (a) The pharmacology of antimalarial drugs. (b) Quinine versus atabrine. (c) 4-amino quinoline drugs with special reference to chloroquine. (d) 8-amino quinoline drugs and the cure of vivax malaria.

(a) *The pharmacology of antimalarial drugs:* Prior to the war the use of antimalarial drugs with regard to dosage and treatment schedules was largely empiric. Commonly employed treatment regimes were the result of clinical trials in patients in various parts of the world, and were rarely the same in any two places. It was obvious that in order to have a baseline for evaluating various agents to be tested in a large scale screening program, standardized infections with known strains, and arbitrarily defined treatment response, would have to be investigated. These studies were largely initiated by Shannon¹ and his group, and rapid progress was made possible by the discovery of relatively simple accurate chemical methods for determining antimalarial drugs in blood and tissues. As a result, one could study the absorption, storage, disposition and excretion of numerous potentially valuable drugs. And, in conjunction with the determination of antimalarial activity in animals and man, it was feasible to work out the optimum treatment or suppressive schedule for the best drugs.

Table I and Figure 1 were furnished by Dr. David P. Earle, Jr., and were prepared from data published by Shannon¹ and his colleagues.* Figure 1 notes the correlation between plasma level and therapeutic effect and the definition of the so-called minimum effective level of

* Reproduced from the Harvey Lectures, 1945-1946 by permission of The Harvey Society.

TABLE I—THE RELATIONSHIP BETWEEN TOTAL DOSAGE, THE MEAN PLASMA CONCENTRATION (FOR 4 DAYS) OF QUINACRINE AND ITS THERAPEUTIC EFFECT IN THE STANDARD BLOOD-INDUCED THERAPEUTIC TRIAL WITH MCCOY VIVAX MALARIA

Total dosage is given rather than priming and daily dosage because of the characteristics of its physiological disposition

Patient	Total dosage	Plasma quinacrine, 4-day mean	Therapeutic result		
			Class I	Class II	Class III
	<i>g.</i>	<i>mg./l.</i>			
Tra	0.7	44			+
Wal	0.7	39			+
Bel	0.7	34			+
Cra	0.7	32			+
Cha	0.7	31			+
Dar	0.85	27			+
Woi	0.7	26			+
Wor	0.7	26			+
Qui	0.7	26		+	
Cas	0.55	25			+
Dav	0.45	24		+	
Far	0.45	23		+	
Hau	0.6	22		+	
Mis	0.6	21			+
She	0.45	21		+	
Eic	0.45	21		+	
Mar	0.35	19		+	
Chi	0.45	19		+	
Lor	0.70	19		+	
Kas	0.60	18		+	
Sch	0.70	18		+	
Ami	0.45	16		+	
Ash	0.75	16		+	
Ger	0.55	16		+	
Coo	0.35	15		+	
Bit	0.35	13		+	
Dem	0.35	13		+	
Sca	0.45	12		+	
Cuo	0.35	10		+	
McB	0.45	8	+		
Sau	0.25	6	+		
Cra	0.25	6	+		
Kel	0.25	3	+		

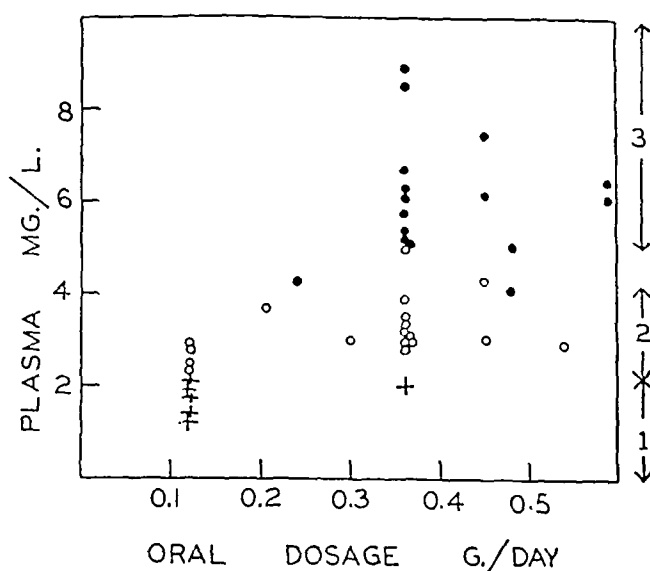


Fig. 1

above 4 mg./L. for quinine, and 30 micrograms/L. for atabrine in a given strain of vivax malaria. From this type of observation and a knowledge of the disposition and excretion of the drugs it became possible by suitable initial and subsequent doses to establish and maintain effective levels for adequate termination of clinical activity.

(b) *Quinine versus atabrine*: It can readily be appreciated that a drug of such historic and established value with world-wide acceptance as quinine would be difficult to displace from the number one position in the treatment of malaria. When atabrine was introduced in 1931, the recommended dose in treatment of acute attacks was 0.1 gram three times daily for 5 days. It was soon found that in many patients fever, symptoms and parasitemia were not promptly controlled with that schedule. As a result there were numerous revisions in dose, and the feeling in many areas was that if atabrine was to be used at all, it should be preceded by several days of quinine therapy for control of the early acute signs and symptoms of the attack. However, when the pharmacology of atabrine was investigated, as indicated, the reason for the relatively poor immediate effect was apparent: The initial small doses were found to be localized in the tissues leaving little in the plasma to exert a chemotherapeutic effect. Ultimately, with continued administra-

tion even on small initial doses, plasma levels are achieved and a satisfactory clinical result is obtained. However, with sufficiently large initial doses an effective level could be created during the first day of treatment, and this level maintained by the serial administration of small doses thereafter. Thus, 1 gram given in divided doses during the first 24 hours, followed by 0.3 gram daily for the next 6 days, provided average daily levels of 41 to 52 micrograms per liter from the second to the eighth day of treatment, and significantly higher levels during the first 24 hours. It had previously been determined by Shannon¹ that with maintained levels of 30 to 40 micrograms per liter vivax infections are promptly controlled. Thus a rational basis for the optimum use of atabrine resulted in the 2.8 Gm. in 7 days schedule we all now know. The clinical effectiveness of this schedule and its superiority over quinine from the standpoint of control of fever, parasitemia, and interval to relapse are summarized from studies by Most and Hayman.² Within 12 hours after the first dose of atabrine some patients already had negative smears, and by 96 hours virtually all were clear. With quinine on the other hand, only 7 per cent were parasite free at 24 hours, and almost a fourth still had parasites at 96 hours. In a few patients parasites persisted for 132 hours. There is little question of the more rapid action of atabrine in clearing the blood of parasites. The contention that quinine controlled fever more quickly than atabrine was not borne out in these studies. It was found that atabrine and quinine were equally effective in relapses; about 10 per cent in each group having fever 24 hours after treatment was begun. But atabrine was superior in primary attacks since only 16 per cent had fever on the second day after its use compared to 32 per cent with fever after quinine.

Since neither quinine nor atabrine are curative drugs, the question of the interval to relapse following treatment, is perhaps of greater importance than initial control of fever and parasitemia. In the case of quinine relapses begin as soon as 10 days after treatment, whereas after atabrine only a few occur in less than 30 days. In large groups of patients studied with Pacific and Mediterranean vivax infections the mean interval to relapse after quinine was 22 days and after atabrine 50 days. Thus, atabrine affords a significantly longer symptom-free interval than quinine, and largely does away with extremely short term relapses.

(c) *4-Amino Quinolines*: The drug of this series which to date has had the most extensive basic and clinical study is chloroquine. Chloro-

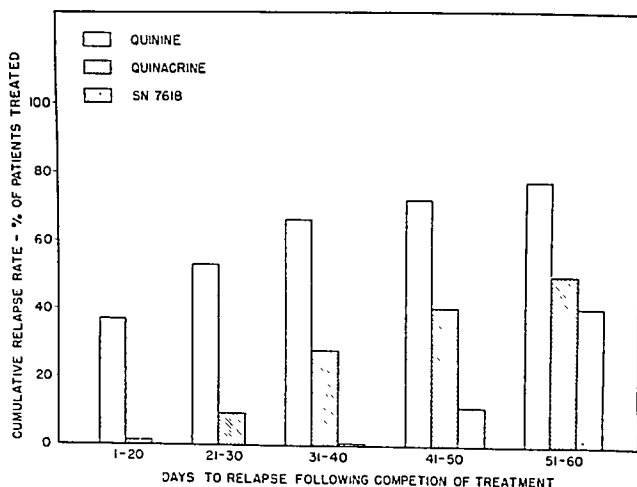


Fig. 2—Interval to relapse following therapy with quinine, atabrine and chloroquine

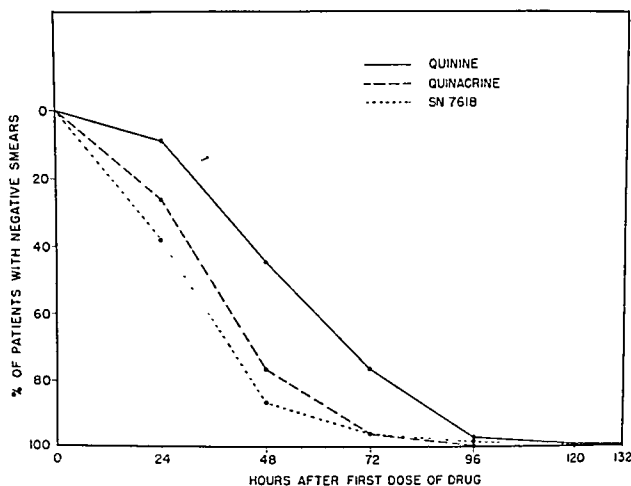


Fig. 3—Effect on parasitemia with quinine, atabrine and chloroquine

quine behaves pharmacologically very much like atabrine except it persists longer in the body. Also from the standpoint of its antimalarial activity, effective levels in the plasma are in the range of 10 gammas per liter, and are achieved with relatively small doses by mouth. As a result of both these properties it is possible to maintain effective suppression by single weekly doses of the drug and to accomplish satisfactory termination of attacks by treatment schedules of from 1 to 4 days.

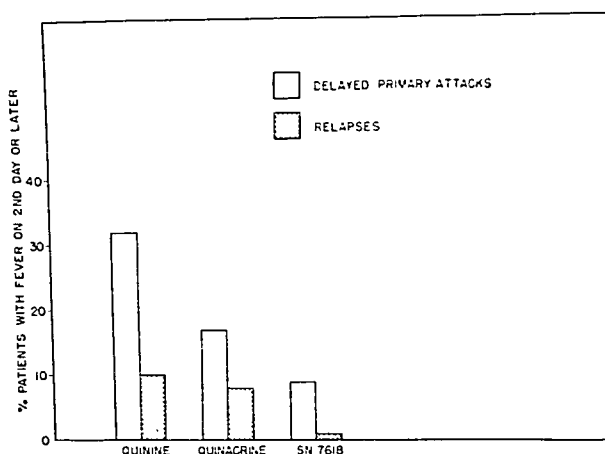


Fig. 4—Control of fever during treatment with quinine, atabrine and chloroquine

Both from the standpoint of short term treatment and suppression it is decidedly less toxic than either atabrine or quinine. Prolonged use does not produce the yellow skin color atabrine does, nor does it produce symptoms of cinchonism. Its effectiveness in controlling parasitemia and fever, and in providing a longer interval before relapse is demonstrated in Figures 2, 3 and 4 in which chloroquine is compared to quinine and atabrine in these respects. The data are from studies by Most and his colleagues³ conducted during the war.

With respect to control of parasitemia, one notes 86 per cent of patients were cleared of parasites by 48 hours and practically all were free by 96 hours. Thus, during the first 48 hours chloroquine is definitely more active than either quinine or atabrine, and after that both are better than quinine. Chloroquine also controlled fever more promptly than quinine or atabrine in primary attacks, regardless of initial parasite density or geographic origin of the infection. Only 2 per cent of patients on chloroquine had fever 24 hours after treatment was begun compared to about 10 per cent for both quinine and atabrine.

With regard to the interval to relapse after treatment, only 1 per cent of chloroquine treated patients had another attack within 40 days after treatment, whereas 67 per cent and 28 per cent relapsed after quinine and atabrine respectively. Thus, short term relapses are virtually abolished with chloroquine. Following its use, only one-sixth of the

relapses which would occur in 4 months took place within the first 2 months after treatment, providing a mean interval to relapse of 61 days compared to 22 and 50 days respectively for quinine and atabrine.

Finally the ease of administration of chloroquine in treatment schedules of 1.0 gram of base in 1 day or 1.5 grams in 3 or 4 days, as well as freedom from noteworthy toxicity, make this drug a most attractive one for suppression and treatment of acute attacks of vivax malaria. Despite the convincing evidence which has been published in behalf of chloroquine many clinicians prefer quinine. The responsibility for poor suppression, toxicity, and short intervals to relapse is theirs. However, the effectiveness of chloroquine for suppression and treatment of various strains of vivax and falciparum malaria in various parts of the world as well as its value by mouth or parenterally in fulminating falciparum infections remains to be determined.

(d) *8-Amino Quinolines and the Cure of Vivax Malaria*: Unfortunately clinical studies with these drugs were not commenced until late in the war. If some of the relatively safe 8-amino quinolines now available had been on hand earlier, we could have been spared the tremendous number of hospitalizations because of vivax malaria. Long before the war it had been shown in India that quinine and plasmochin given concurrently favorably reduced the relapse rate in vivax malaria. However, plasmochin was considered by many too toxic for extensive routine application for the required period of therapy. In military hospitals in this country the use of plasmochin for 3 to 5 days after quinine or atabrine for acute attacks of malaria, did not result in a reduction in subsequent relapse rates. Following the demonstration of the curative properties of combined quinine-plasmochin therapy in volunteers with mosquito induced vivax infections in the United States, a clinical study at Moore General Hospital in this country was undertaken and reported by Most⁴ and his colleagues in November 1946. Originally 72 patients were treated and observed for more than 6 months, but since then approximately 100 patients have been treated and adequately followed. Clinical relapses occurred in only 4 per cent of treated patients compared to relapses of 80 and 90 per cent for similar groups treated with quinine, atabrine, chloroquine or other drugs. Except for abdominal cramps in most patients and methemoglobinemia or mild anemia and significant leukopenia in a small number of patients, no serious toxic reactions occurred. Treatment was completed in all cases. Each dose

of quinine was 0.6 Gm. and each dose of plasmochin was 0.02 Gm. of the naphtholate. Both drugs were given together at 8 hour intervals for 14 days. Although this dose of plasmochin does not cure a high proportion of heavy experimental infections, our dose was nevertheless curative possibly because of modification of the infection by prior suppression with atabrine. It should also be emphasized that the patients were in good physical condition, were hospitalized during treatment, and were all white. This is noted since the incidence of severe hemolytic reactions from plasmochin is more common in negroes and other pigmented races.

More recently, 8-amino quinolines, which in experimental human infections are more active and less toxic than plasmochin, have been introduced. Of these pentaquine and isopentaquine have been most intensively studied by Alving⁵ and his colleagues. More than 500 veterans with relapsing vivax malaria have been treated with 10 mg. of pentaquine base and quinine at 8 hour intervals for 14 days. In New York Straus and Gennis⁶ had only one failure in 50 patients so treated and adequately followed afterwards. Coggeshall⁷ in Chicago has treated about 400 men with combined pentaquine-quinine on an out-patient basis. There can be little question that these drugs are curative and represent a major advance in the cure of vivax infections. Thus, as a result of the wartime necessity and interest in malaria, it is now possible to effectively suppress, treat, and cure malaria.

AMEBIASIS

The average incidence of infection with *E. histolytica* in the United States has been widely published as being in the range of 10 per cent of the population, with variations from 1 to 40 per cent or more for various parts of the country. Stool surveys conducted at military separation centers and military hospitals in the United States indicated that probably 5 to 15 per cent of veterans who served in the Pacific Theaters are infected with this parasite. In this city Shookhoff⁸ has reported an infection rate of about 10 per cent in Pacific veterans. The speaker has found 8 per cent of veterans from various Philippine Islands carrying *Endamoeba histolytica*. Study of a cross section of veterans in the city in various clinics and hospitals without consideration of geographic areas of service or symptoms indicates that probably not more than 4 per cent have amebiasis. It is apparent, then, that from the standpoint

of treatment, amebiasis is an important infection, even if one overlooks the clinical and epidemiologic implications.

The number and diversity of drugs available for the treatment of amebiasis, and the need in many cases, of parenteral, oral and/or intra-rectal therapy, as well as prolonged treatment with more than one drug, is ample evidence of the desirability of having more effective amebicidal agents than are now at hand. In the following Table are listed the more important standard drugs used in the treatment of amebiasis as well as several recently introduced agents. I shall briefly review the present status of these drugs.

TABLE II—DRUGS USED IN TREATMENT OF AMEBIASIS

(a) EMETINE	(d) 4-AMINO QUINOLINES
(b) IODO-QUINOLINES	1. Chloroquine
1. Chiniofon	
2. Diodoquin	(e) ANTIBIOTICS
(c) METALS	1. Para-amino-benzoic Acid
1. Carbarsone	2. Bacitracin
2. Thioarsenites	3. Aureomycin
3. Wia	

(a) EMETINE:

This drug has been the stand-by for a long time in the treatment of clinically severe amebic colitis, and amebic hepatitis or abscess, as well as other forms of extra-colonic amebiasis. Satisfactory, often dramatic results are well known from the use of emetine. However, potential toxicity from prolonged or exaggerated use, a high failure or relapse rate in cases in which it alone is used, and apparent resistance of some severe recurrent or chronic cases leave much to be desired from emetine as a universal amebicide. At the present time emetine is used in daily doses of 0.06 Gm. for from 4 to 7 days in clinically severe or moderately severe amebic colitis, and from 7 to 10 days in amebic hepatitis or abscess, granuloma of the colon, pulmonary, brain or skin involvement. A similar course may be given after the lapse of 10 days, but some thought should be given to possibly severe toxic reactions before a third course is given. In this connection it might be of interest to point

out that during the war, emetine was extensively used in the American military forces, often at the dispensary level, in men who carried out their usual duties including aircraft operation. Yet, as far as I know, not a single death from emetine was reported during World War II. One should not encourage the indiscriminate use of emetine, but I think that many of the serious reactions described have resulted from large doses, prolonged therapy, intravenous use, severe chronic debilitation or other serious underlying constitutional disorders.

(b) IODO-QUINOLINES:

This class of compounds, of which chiniofon and diodoquin are but two, have gained widespread acceptance in the treatment of amebiasis. Until recently the basis of their activity has been attributed by many to their iodine content. Thus diodoquin has been said to be more effective than chiniofon, because it contained twice the iodine content of the latter, and yet, daily dosages for both are about the same, or greater, in the case of diodoquin. Diodoquin does not produce the diarrhea which frequently accompanies chiniofon therapy, and for that reason is preferred by many clinicians. In a few instances iodism has been observed in the course of prolonged diodoquin medication. Currently total daily doses of 3 grams by mouth for 20 to 30 days are advocated, and longer treatment, or several courses may be necessary in some cases, particularly those with granulomas. In clinically severe amebiasis with extensive or slowly healing ulcers, or well-established cecal deformities or granulomas, retention enemas of chiniofon are considered by some individuals a valuable adjunct to simultaneous oral iodoquinoline and parenteral emetine therapy; 200 to 700 cc. of a 2½ per cent suspension are given in one or more courses of 7-10 days each. Although cure rates from these drugs are said to be 80 to 95 per cent, critical prolonged follow-up studies in large groups of patients with infections acquired in widely scattered geographic areas are not available. As a matter of fact, whether or not it represents lack of confidence in one or all the drugs one cannot say, but the vogue in the treatment of amebiasis in many parts of the world and in this country is to use all available drugs, some simultaneously, and others serially and in rotation for several courses. In this way one hopes to overcome the shortcomings of any one agent and to produce a cure without the need for further study of the patient's stools.

(c) METALS:

1. *Carbarsone* like diodoquin and chiniofon has had widespread acceptance in many parts of the world as a suitable amebicide. Although cure rates for this drug are considered to be approximately those of the iodoquinolines, the limitations of prolonged observation of large groups of patients mentioned for the latter are applicable to carbarsone. The original dosage schedule for intestinal infections, namely 0.25 Gm. twice daily for 10 days, is adhered to by most clinicians who use carbarsone before or after one of the iodo-quinolines. With regard to the toxicity of carbarsone and the reluctance of many physicians to use this drug if hepatitis is suspected, it can be pointed out that in subjects studied at the National Naval Medical Center, no evidence of hepatic or kidney dysfunction was observed with daily doses 5 times greater than the standard dose. During the war and since we have used daily doses of 1.0 Gm. without toxicity. It is possible that increased doses of carbarsone may significantly increase its efficiency. But here again there is need for a critical re-evaluation of these agents.

2. *Thioarsenites*: For some time Hamilton Anderson and his colleagues have been studying various arsenicals in the treatment of amebiasis. Recently they have found a group of thioarsenites which they feel to be superior to carbarsone on the basis of monkey and human observations in this country and in Costa Rica. Of 40 patients treated, all but 2 were reported free of infection. The total number of patients treated and adequately followed is still not sufficiently great to recommend these drugs, nor has the question of toxicity, especially gastrointestinal, been completely worked out.

3. *Wia*: This drug containing both bismuth and arsenic in organic form was first reported on by Hauer⁹ in 1943. Wia alone or in combination with chiniofon when tested in German troops of the Afrika Korps was said to eliminate cysts from the stool promptly, but was not satisfactory in acute virulent infections. More recently Berberian¹⁰ reported cure of 24 out of 25 patients treated with Wia alone compared to 5 of 11 treated with chiniofon, and 33 of 38 were cured after treatment with Wia and chiniofon combined or alternated. No side effects are reported. Whether or not this drug will have an important position in the therapy of amebiasis one cannot say at this time, but preliminary observations in this city with daily doses of 1.5 Gm. for 7 days are encouraging.

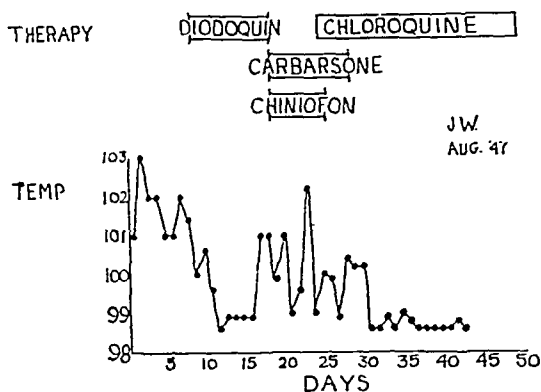


Fig. 5—Temperature chart in case II treated with chloroquine

(d) 4-AMINO QUINOLINES:

Chloroquine: Conan¹¹ demonstrated that chloroquine has a moderate degree of amebicidal activity in intestinal infections. In a series of 32 patients treated with 0.3 gram of base for 21 days and adequately followed after treatment, cures were effected in 50 per cent of the patients. This is an important observation not necessarily in relation to the use of chloroquine in colonic amebiasis, but rather in relation to the fact that the basis of activity of the so-called organic iodides may be the quinoline nucleus, and if this is so, a new group of compounds is available for investigation. In this connection, a recently developed technique of infecting young rats by intracecal inoculation of cultures of amebae represents an important advance in the experimental chemotherapy of amebiasis. Large scale screening tests in industrial and university laboratories now in progress may provide us with agents which are universally active in all forms of amebiasis, and which otherwise may have been discarded because of poor *in vitro* activity.

In addition to the amebicidal activity of chloroquine in some cases of intestinal amebiasis, Conan¹² also has demonstrated chloroquine to have a very high degree of activity in acute amebic hepatitis and abscess. In one of these patients emetine had failed to control the infection. Others have observed equally good results with chloroquine in hepatitis. Figures 5 and 6 are illustrative of the response to chloroquine in 2 patients. The first case was presented by Murgatroyd and Fairley¹³

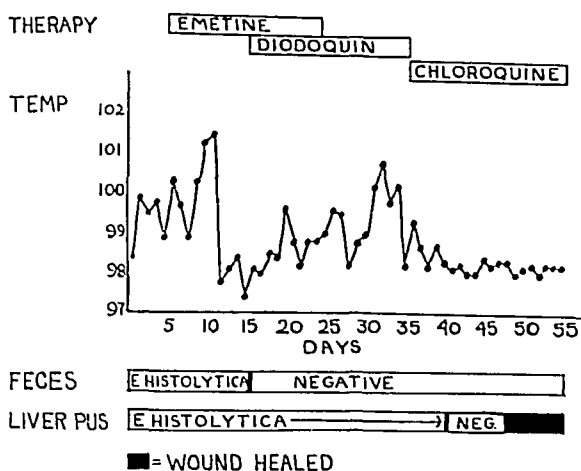


Fig. 6—Murgatroyd and Fairley's case treated with chloroquine

in London, and the data for the slide were sent to Dr. Conan who prepared it. The patient had an amebic abscess of the liver and was drained 4 months previously. He did not respond to emetine parenterally, by mouth or irrigation of the abscess cavity, although emetine and diodoquin cleared his intestinal tract of amebae. He received 0.75 Gm. chloroquine by mouth for 18 days. Within 4 days the liver pus contained no amebae, and within 12 days the wound was healed. Fever was controlled promptly.

The second case was treated at the Veterans Hospital, New York. The patient had a large tender liver, fever, leukocytosis, amebae in the stools, and a positive complement fixative for amebiasis. He was given 0.6 Gm. chloroquine by mouth for 2 days, and 0.3 Gm. daily for the next 19 days. The response was prompt and recovery complete. If these results are borne out in larger groups of patients in various parts of the world, and if one appreciates the ease of oral medication with chloroquine, and the freedom from significant toxicity, then this finding may represent a noteworthy contribution to the treatment of amebiasis.

(c) ANTIBIOTICS:

1. *Para-amino-benzoic acid*: Dwork¹⁴ (1948) reported apparent cure of 4 of 9 patients with intestinal amebiasis treated with para-amino-

benzoic acid. The frequency and the size of each dose as well as the relatively poor cure rate observed would preclude its general use in the treatment of amebiasis. However, the fact that para-amino-benzoic acid possesses some activity is important from the standpoint of the possible antibiotic mode of action of other agents unrelated to those now in use.

2. *Bacitracin*: The background for the use of bacitracin in the treatment of amebiasis is of interest. For a long time many investigators have attempted to culture *Endamoeba histolytica* free of bacteria. Although the solution has not been resolved, some progress has been made with heat killed filtrates and dead bacteria, along with the use of penicillin and streptomycin in cultures. In order to determine whether bacitracin might help eliminate or reduce the bacteria in the amebae cultures it was studied in E. C. Faust's¹⁵ laboratory at Tulane and found to inhibit or kill the amebae to a greater degree than the accompanying bacteria. Alfred Longacre,¹⁶ Louisiana State University, then treated patients with amebic colitis using bacitracin in divided doses orally. He noted excellent clinical response with disappearance of amebae from the stools and rapid healing of ulcers in some patients. In this city, Most, Grossman, Miller and Conan¹⁷ have confirmed the observations of Longacre in both acute clinical cases and in non-symptomatic carriers. Currently total daily doses by mouth of 40 to 160,000 units for 10 to 20 days are being studied, but it is possible optimum treatment may require greater doses for more than 20 days in some cases. Apparently bacitracin is not absorbed, and no significant toxicity or symptoms have been noted from its oral use. We have treated more than 50 patients to date, and cure rates of 60 to 80 per cent are probable on the basis of mean observation periods of 6 months after therapy. In severe dysentery, clinical response may be dramatic in a few days with cessation of diarrhea, healing of ulcerations and disappearance of *E. histolytica*. It is of great interest that in some such cases the amebae reappear in the stools days to months after therapy has been completed, but the patient has no demonstrable lesions and is symptom-free. Bacitracin is known to result in disappearance of gram-positive organisms and anaerobes from the stools. It may be that the initial lesions are produced by *E. histolytica*, but are enlarged to clinical significance by these bacteria; or the bacteria furnish essential metabolites for the growth or virulence of *E. histolytica*. In either case bacitracin

apparently influences the bacterial parasite relation in the colon to the benefit of the patient in a significant number of instances.

3. *Aureomycin*: More recently we have treated patients with amebiasis with 20 Gm. of aureomycin given by mouth during 10 days. To date, of 8 patients so treated 7 have remained free of *E. histolytica* following therapy.

HELMINTHS

In general with several notable exceptions the status of the therapy of the common helminths is satisfactory. Advances are represented by the introduction of new drugs or the revision of treatment schedules or techniques with drugs of established value. My remarks will be limited to the status of the therapy of the worms most often encountered by the practitioners in this country.

THE NEMATODES OR ROUNDWORMS

Of the more common roundworms, the treatment of *Ascaris* with hexylresorcinol and *Enterobius*, or pinworm, with gentian violet is on the whole satisfactory, although a drug less toxic and given for a shorter time than gentian violet would be desirable against the pinworm. Tetrachlorethylene has been considered the drug of choice in the treatment of hookworm infections. However, during and after the war it was noted that many patients were still passing hookworm eggs in the stools, in spite of having had during a period of months, from one to twelve treatments with tetrachlorethylene. Most and Hayman¹⁸ reported that almost all the adult worms recovered from such patients were *Ancylostoma duodenale* rather than *Necator americanus*, the hookworm of this country. In the same study it was found that only 25 per cent of patients treated for the first time for hookworm and found to have *Ancylostoma* infections were cured by a single course of 3 to 5 cc. of tetrachlorethylene. These patients were almost exclusively from various Pacific Islands. In contrast to this poor result similar doses of tetrachlorethylene cured more than three-fourths of *Necator* infections. Since the vast majority of hookworm infections were light and did not represent hookworm disease, the difficulty in the elimination of *Ancylostoma* in patients in this country is not serious. One should consider the areas of exposure if results of treatment are poor, and also in well sanitated areas the actual need for re-treatment is negligible. Certainly

the potential risks from carbon tetrachloride and oil of chenopodium in full doses, although these drugs may be more effective against *Ancylostoma*, do not warrant their use in this country. However, the persistence of *Ancylostoma* in spite of tetrachlorethylene therapy raises the possibility of its introduction into the southern United States.

Strongyloides and *Trichurus* infections which are relatively common in some parts of the United States, and particularly *Trichurus* in Pacific veterans, deserve comment. In the case of *Strongyloides*, treatment with 3 daily doses of 60 mg. each of gentian violet for 16 days is the standard textbook recommendation. However, if patients are followed carefully, it will be found that in a large number larvae reappear in the stools within several months after treatment. It should also be known that the commonly used preparation of gentian violet is designed to disintegrate 4 hours after ingestion, but the adult worms we seek to kill are high in the small intestine. D'Antoni¹⁹ originally advocated larger doses of gentian violet. We have found increasing each dose by one pill each day until the maximum number tolerated, usually 12 to 16 per day, are taken for about 2 weeks, produces a satisfactory result in a high proportion of cases treated. In the case of *Trichurus* which rarely produces, in this country at least, disease or symptoms, treatment is unsatisfactory. In areas where fresh leche de higueron, the latex of several species of fig tree, is available it is used with moderately good results in eliminating the infection. Recently²⁰ in this country enteric tablets of emetine hydrochloride have been used experimentally with excellent results in eliminating *Trichurus* adults from the large bowel. However, in some patients dislodgment of the anterior portions of the worm brings with it a bit of mucosa in which it is embedded and bloody diarrhea may result. The preparation of emetine used is not commercially available, and further study of efficacy and toxicity would appear necessary before it could be recommended against a relatively harmless parasite. Ferric ammonium citrate, 50 per cent solution, in oral doses of 12 cc. daily has been reported to reduce egg counts 80 to 90 per cent, but actual cure rates are not known. The author has treated several cases but observed no cures, although during therapy the egg counts were markedly reduced.

Unfortunately no specific drugs are available for the treatment of trichinosis. Hetrazan, which will be discussed shortly in relation to its use in the treatment of filariasis, has not given conclusive results in a

sufficiently large number of cases of acute trichinosis to permit its evaluation at this time.

Filariasis, while no longer a problem in the United States, is of interest to us because of its prevalence in the Virgin Islands and Puerto Rico and as a result of the war its occurrence in several thousand members of our military forces. Fortunately almost all the latter infections were not severe, and are no longer clinically or otherwise detectable. Whether later on any of these men may develop elephantiasis or other sequelae of filariasis no one can say, but certainly there is no indication for any treatment except perhaps in some case reassurance. Nevertheless, a tremendous amount of effort was devoted to the investigation of possible filaricidal drugs. The number studied and results have been voluminously published, and will not be reviewed here. Various antimony and arsenic preparations were found effective in destroying the adult worms in the cotton rat, and in producing disappearance or reduction of microfilariae from the blood of man within 6 to 12 months after treatment. Neostibosan is perhaps the most effective and least toxic of these metallic agents. Undoubtedly the reduction in the total number of circulating microfilariae available to transmitting arthropods, in conjunction with antimosquito measures is important from the standpoint of the control of filariasis. More recently, Santiago-Stevenson, Oliver-Gonzalez and Hewitt²¹ reported the use of "Hetrazan" (diethyl carbamyl piperazine) in Puerto Rico in 26 patients demonstrated to have microfilariae in the peripheral blood. The daily doses ranged from 0.5 to 2.0 mg./kg. administered for from 3 to 22 days. Microfilariae disappeared completely or were markedly reduced in all patients within a few days, and in 4 patients nodular tender swellings with lymphadenitis of spermatic cord or extremities suggested accompanying deaths of adult worms. No significant toxic manifestations attributable to the drug were observed. In the treatment of another form of filariasis, namely onchocerciasis in which the adult filaria worms are in subcutaneous nodules, severe local and systemic reactions even from very small doses of Hetrazan have been reported. These are presumably due to gross rapid destruction of numerous adult worms and liberation of foreign protein. Certainly the use of neostibosan and Hetrazan in the treatment of filariasis are notable chemotherapeutic contributions, but their exact place in the clinical therapy of various forms of filariasis is not yet defined.

CESTODES OR TAPEWORMS

I shall concern myself only with the beef tapeworm, *Taenia saginata*, since it is the most commonly encountered tapeworm in private practice in this part of the country and because its elimination is often not accomplished with ease. Until recently, oleoresin of aspidium has been considered the drug of choice in the treatment of all the intestinal tapeworms of man. In my experience most treatment failures are due to the use of other drugs of less efficiency, or to the use of inadequate amounts of oleoresin of questionable potency administered in capsules. If 8 grams of fresh oleoresin of aspidium is introduced into the duodenum by tube together with 30 to 45 grams of sodium sulfate and about 100 cc. of water, the probability of cure is at least 90 per cent. Preliminary purgation and a low residue diet for 24 hours previously and treatment in the fasting state facilitate recovery of the head if it is passed. Even if the head is not found, there is no need for re-treatment before 6 to 12 weeks, or until segments are again noted in the stools. In some patients the head is passed after treatment but not found, and cure is determined by a suitable period of post-treatment observation. I have not noted any significant toxicity from 8 to 12 grams of oleoresin of aspidium given as described in more than 50 patients.

Shortly before the war following Culbertson's²² report of the beneficial effects of atabrine in a tapeworm infection of mice, I treated 4 patients with tapeworms with 0.6 to 1.0 Gm. of atabrine administered in solution intraduodenally. In one patient a brightly stained yellow complete worm was recovered. In another case an unstained worm without the head was passed, but follow-up of the patient for 4 months suggested probable cure. The other 2 patients who received 0.6 and 1.0 Gm. respectively were definite failures. During this year, Brown²³ in a review of anthelmintic therapy reported cures in all of 8 patients with tapeworms treated by Shookhoff with 0.8 or 0.9 gram of atabrine given in divided doses by mouth. Failures resulted from treatment of 3 children presumably because of vomiting. I know of 7 definite cures of 13 other patients treated with atabrine by mouth or intraduodenally, although the actual cure rate may be higher since the outcome in the remaining patients is unknown. In the same review Santiago-Stevenson is said to have noted excellent results in a small number of patients treated with 1.0 Gm. of crystalline hexylresorcinol administered intraduodenally. If this observation is confirmed and cure rates of 90 per

cent or more are reported, such treatment would be a distinct advantage because of the availability and stability of hexylresorcinol compared to oleoresin of aspidium. At the present time I think that the latter drug is the most reliable agent against tapeworms. Atabrine is simple to give if vomiting doesn't occur, but single doses of 0.8 to 0.9 gram may produce other undesirable toxic reactions. Its further trial is indicated.

THE TREMATODES OR FLUKES

The schistosomes, principally *S. mansoni* and *S. japonicum*, are the flukes which should interest us; the former because of the significant incidence of infection in Puerto Rican residents in this country, and the latter because of our military experience in the Philippines during the war. With regard to schistosomiasis japonica, one must note that approximately 1500 men contracted the infection on Leyte, and were hospitalized both abroad and in this country for study and treatment. Probably an equal, if not greater number also were infected but not recognized because of the mild original manifestations of the infection. The third group of infections occurred amongst 2000 or more American military prisoners of the Japanese interned in prison camps at Davao and elsewhere in the Philippines. The extent to which these men were infected is unknown, but a preliminary random sampling by examination of one to three stool specimens indicates the percentage to be very high.

The principal drugs used before the war in the treatment of schistosomiasis were trivalent antimony preparations, fuadin and tartar emetic. Fuadin, named after King Fuad of Egypt, was introduced by the Germans for the treatment of vesical schistosomiasis due to *S. haematobium*. The original dosage schedule of 40 cc. as a course of treatment seemed satisfactory in Egypt, though the problem of reinfection and short term observations of patients did not permit exact evaluation of its efficiency. In *S. mansoni* infections 40 cc. possibly cured more than 50 per cent of patients, and later better controlled observations indicated that 70 cc. probably cured more than 75 per cent of patients. During the war the effect of fuadin on *S. japonicum* infections was not known. The majority of our patients received overseas one or more courses of 40 cc. of fuadin. Yet we found that following treatment of cases passing viable eggs on arrival in this country with 70 cc. of fuadin the failure rate was 80 per cent. Increasing the total amount to 100 cc. but adhering to the

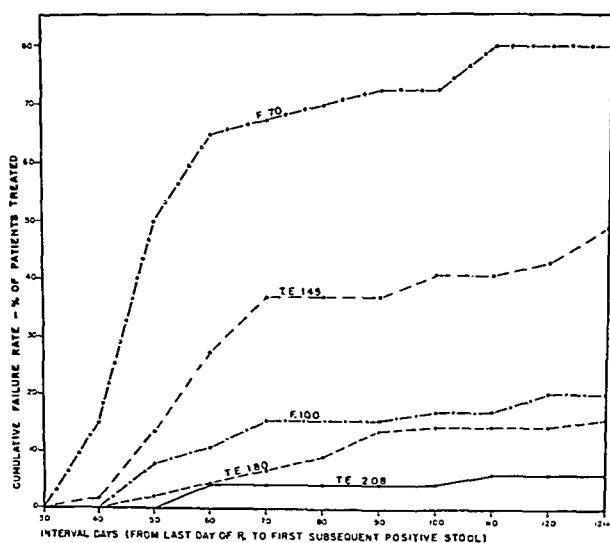


Fig. 7—Results of treatment of schistosomiasis japonica with fuadin and tartar emetic

alternate day schedule of 5 cc. per injection did not lower the failures materially. However, by giving 8 cc. daily until 100 cc. of fuadin had been injected the failure rates were sharply reduced. With equivalent amounts of antimony in tartar emetic the results were better on all treatment schedules as shown in the accompanying Figure 7. Thus with 1.45 Gm. of tartar emetic the failures were 50 per cent, and as the total dose was increased the failures were decreased until in a group receiving 2.2 Gm. or 444 cc. of $\frac{1}{2}$ per cent solution of tartar emetic the failures were negligible. We now recommend this amount in *S. japonicum* infections, and 500 cc. in patients with central nervous system involvement or failure following the initial course of treatment. Tartar emetic is more toxic than fuadin and more troublesome to administer since the solution should be freshly made and must be given slowly intravenously, whereas fuadin is given intramuscularly. In *S. mansoni* infections we recommend 5.0 cc. doses daily, or as closely spaced as possible until 100 cc. are given. Stool examinations should be started a month after completion of therapy and continued weekly for at least 6 months or more using techniques specially devised for schistosome eggs.

Several years ago, Alves and Blair²⁴ reported a high percentage of

especially adept in describing these historic encounters and this he does accurately and impartially, even at times with a delightful humor.

In the succeeding chapters which relate the events and developments of the Academy under its successive presidents, the author has selected so wisely that the reader is granted a perceptive appraisal of the great actors in New York Medicine as well as of significant advances in medicine during the first hundred years of the Academy. Each chapter deals with the term or terms of one or more Presidents and thus we come upon such stirring names as Valentine Mott, Willard Parker, Austin Flint, Fordyce Barker, Abraham Jacobi, Alfred L. Loomis, Joseph D. Bryant, Edward G. Janeway, Charles L. Dana, Walter Belknap James, George David Stewart, Samuel Waldron Lambert, Bernard Sachs, Eugene H. Pool, James Alexander Miller and William Worthington Herrick, to name only a few of the departed leaders whose lives have influenced the progress of medicine in America.

Characteristic of the narrative qualities of this history is the description of the great battle waged during the third term of office of President Fordyce Barker. In appealing to the Fellowship for support Dr. Barker said in summary: "I think that it will be apparent that the whole intent of the proposed amendments is to make the Academy of Medicine a purely scientific society, independent of all other organizations; to place its standard of ethics on a higher plane than before; and to prevent the possibility of any future troubles by the introduction of matters foreign to its advanced objects."

The opposition included such men as the Austin Flints, Sr. and Jr., John H. Hinton and Samuel Purple. A long and bitter struggle followed. In the end the course of Fordyce Barker was sustained. Characteristically the incident is summarized by the author of this book: "The whole thing was a miserable, unfortunate affair, but it established, for all time, the Academy's position as an organization devoted to scientific matters, aloof from all standards of ethics, except as affecting its own organization. It was perhaps worth while."

As the history progresses it becomes apparent that the Academy, which in its beginning could have been described as an exclusive doctors' club, has through the years both broadened and elevated its mission so that more and more it has become an organization dedicated to medical education, public health and the welfare of mankind.

The book is replete with incidents of interest to the profession and

BULLETIN OF THE NEW YORK
ACADEMY OF MEDICINE

CONTENTS

Advances in Diagnostic Methods	747
<i>Benjamin P. Watson</i>	
Diagnostic Significance of Electrolyte Disturbances . .	749
<i>John P. Peters</i>	
The Present Status of Clinical Electroencephalography	764
<i>Frederic A. Gibbs</i>	
A Chronicle of One Hundred Years of Otolaryngology	775
<i>A. C. Furstenberg</i>	
Section on Microbiology:	
Chemistry of Chloromycetin, <i>H. M. Crooks, Jr.</i>	792
Clinical Use of Synthetic and Fermentation Chlor- amphenicol (Chloromycetin), <i>Joseph E. Smadel</i>	794
Clinical Use of Chloramphenicol (Chloromycetin) in Certain Bacterial Infections, <i>Theodore E.</i> <i>Woodward</i>	795
Library Notes:	
Recent Accessions to the Library	795
Index, 1949	797

AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

MAHLON ASHFORD, *Editor*

Published Monthly by THE NEW YORK ACADEMY OF MEDICINE
2 East 103 Street, New York 29, N. Y.

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BULLETIN OF
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DECEMBER 1949

ADVANCES IN DIAGNOSTIC METHODS

BENJAMIN P. WATSON

President, The New York Academy of Medicine

O

n behalf of The New York Academy of Medicine I welcome you to this, its Twenty-Second Graduate Fortnight.

The Academy Committee on Medical Education, working through its sub-committees, has always had the responsibility for arranging the programmes. Last year it broke with tradition in selecting "Advances in Therapy" as the general theme in place of, as formerly, submitting a program dealing with diseases related to a particular organ or system. This year the Committee has followed up that break by choosing "Advances in Diagnostic Methods" as a title. This sequence might, in undergraduate teaching, seem to be a little like putting the cart before the horse, but for an informed gathering such as we always have here that is of no consequence.

In the last few years advances in diagnostic methods have been just as notable though perhaps not so sensational and dramatic as those in therapy. To keep pace with those advances in either field requires study and effort on the part of everyone of us, but the effort probably has to

* Opening address, 22nd Graduate Fortnight of The New York Academy of Medicine, October 10, 1949 by the President of the Academy.

be greater in informing ourselves on up-to-date diagnosis, than in applying intelligently the newer therapies.

Even in the days when diagnostic methods were what we regard now as few and crude, the medical student regarded the time spent upon their acquisition as altogether out of proportion to that devoted to treatment. It was only after entering upon the practice of medicine that he realized the importance of these early disciplines in diagnosis.

I can go back to the time when percussion and auscultation were practically the only methods used in the appraisal of cardiac lesions, and the latter practiced through a wooden stethoscope; when there was still debate as to whether blood pressure readings were valid or were of any significance; when a fracture was diagnosed by eliciting crepitus; when the leukocyte count was just beginning to be regarded as of value in the diagnosis of inflammatory lesions; when chemistry was employed only in simple examination of urine or gastric content; when the material obtained by a diagnostic curettage was interpreted as pathological, when in many instances, as we now know, it showed only normal physiological variation.

Glancing over our program for this Fortnight we realize what advances have been made since those days. We now have electrocardiography, cardiac catheterization, angio-cardiography in the diagnosis of diseases of the vascular system; the detailed examination of the blood elements and bone marrow biopsies in blood disorders; renal function tests, liver function tests and liver biopsies; radiologic techniques in the investigation of the gastro-intestinal tract; electro-encephalography in the elucidation of brain pathology; new methods of attacking the problems of bacterial and virus infections and lastly the use of isotopes in throwing light upon all sorts of physiological and pathological states.

The program made up of evening lectures, morning panel discussions and afternoon hospital clinics, is designed to give all of us a general understanding of the advances made in diagnosis in all branches of medicine and at the same time to supply a more detailed and practical exposition to those who are especially interested in particular fields.

I cannot name individually all those who have worked on the planning of this Fortnight or those who are contributing to it, but we should like each of them to know that the Academy is deeply grateful for the time, thought and effort expended.

DIAGNOSTIC SIGNIFICANCE OF
ELECTROLYTE DISTURBANCES*

JOHN P. PETERS

Professor of Internal Medicine, Yale University School of Medicine

PERHAPS the title chosen for this talk is too broad. Actually, I shall discuss chiefly the sodium salts of blood with brief mention of potassium. If the chemical pattern of normal serum (see Figure 1) is examined, it can be seen at once that 90 per cent of the total electrolyte is composed of sodium salts of which, in turn, more than 90 per cent consists of chloride and bicarbonate. The membranes of the cells of the body are almost impervious to electrolytes, but allow the free passage of water. It follows that the osmotic pressure in all media of the body will be the same and that the distribution of water between the cells and the extracellular fluid will be determined chiefly by the relative concentration of salts in the two media respectively. Since the materials in the cells can only be secured from the extracellular fluid and appear to enter and leave the cells only in connection with metabolic processes, salts of the extracellular fluid, of which serum is a part, play the major role in controlling the distribution of water. Of these, sodium salts are overwhelmingly the most important, not only because of their high concentration, but also because movements of sodium appear to be attuned to the automatic adjustment of exchanges of water. If the concentration of sodium in serum and extracellular fluid (hereafter concentrations in serum only will be mentioned because they mirror precisely concentrations in extracellular fluid, of which serum is a part) rises, the cells will give up water to equalize osmotic pressure. They will, therefore, contract, their contents becoming relatively dehydrated or overconcentrated, while the extracellular fluid will expand proportionally. If the concentration of sodium in the serum falls, the cells will take up water from the extracellular fluid. They will, therefore, swell, their contents becoming more diluted. These changes in the concentration of the cellular contents in response to osmotic influences appear to have two

* Given October 11, 1949 before the 22nd Graduate Fortnight of The New York Academy of Medicine.

paratively simple methods. From the figure it is evident that in normal persons the concentration of chloride + bicarbonate is so nearly equal to that of sodium that, if chloride and bicarbonate are known, the concentration of sodium can be established with sufficient accuracy for all clinical purposes. This is not, however, true in a large proportion of disease conditions, because in these disorders other acids accumulate in the blood to displace bicarbonate. Among these we recognize ketone acids in starvation and in diabetes, lactic acid when oxygenation of the tissues is impaired, phosphates and sulfates in severe renal decompensation. The pattern of the serum when such acids accumulate is illustrated in the center of Figure 2, compared with that of average normal serum on the left.

In this and most of the other figures, only the concentrations of sodium, chloride and bicarbonate are given, because these are the only measurable ions that need concern us for the moment. The total height of each column represents sodium, the open area chloride, the vertically lined area bicarbonate, and the stippled area at the top the difference between sodium on the one hand and bicarbonate + chloride on the other. This may be termed the *undetermined acids*. This component, as I said before and as you can see from the figure on the left, in normal persons is quite small. It is also relatively constant. The middle column illustrates the simplest condition encountered in diabetic acidosis, the accumulation in the serum of ketone bodies, β -hydroxybutyric and acetoacetic acid, which have displaced bicarbonate. Under these circumstances it is quite impossible to estimate the concentration of sodium from bicarbonate + chloride without ascertaining the concentration of the undetermined acids, which is not feasible. From the sum of bicarbonate + chloride it would be inferred that sodium was greatly reduced, whereas in point of fact it is quite normal. From the standpoint of therapy it is highly important to ascertain whether or not sodium is depleted. There are two types of acidosis; the one that has just been described and which is depicted in the center of the figure, in which bicarbonate is displaced by a foreign acid; and the one on the right in which there is an actual deficit of sodium. As they have been drawn, the concentrations of bicarbonate + chloride, from which sodium is usually estimated, are identical in the two figures. The condition illustrated on the right constitutes the clearest indication for the administration of sodium bicarbonate because there is a deficiency of

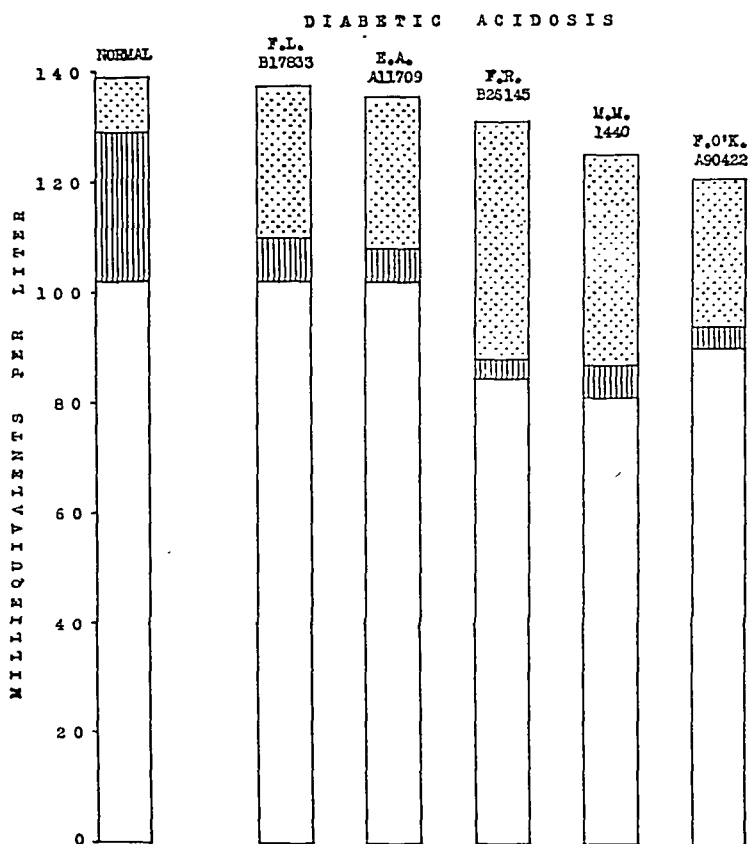


Figure 3—Electrolyte patterns of sera in diabetic acidosis. The total height of each column represents the concentration of sodium, the open portion chloride, the vertically lined portion bicarbonate, the stippled portion “undetermined acids.” The pattern of average normal serum is illustrated on the left.

both sodium and bicarbonate. The condition in the center does not. Administration of sodium bicarbonate in this state, though it may restore to normal the concentration of bicarbonate, can do so only by producing an excessive concentration of sodium in the serum, an undesirable disorder. This is shown by the dotted extensions to the columns, which illustrate the effects of adding to each serum sufficient sodium bicarbonate to restore the normal concentration of bicarbonate in the serum. The proper treatment of the condition in the center is to facilitate the utilization and excretion of the abnormal acids which have displaced bicarbonate. In diabetes this can

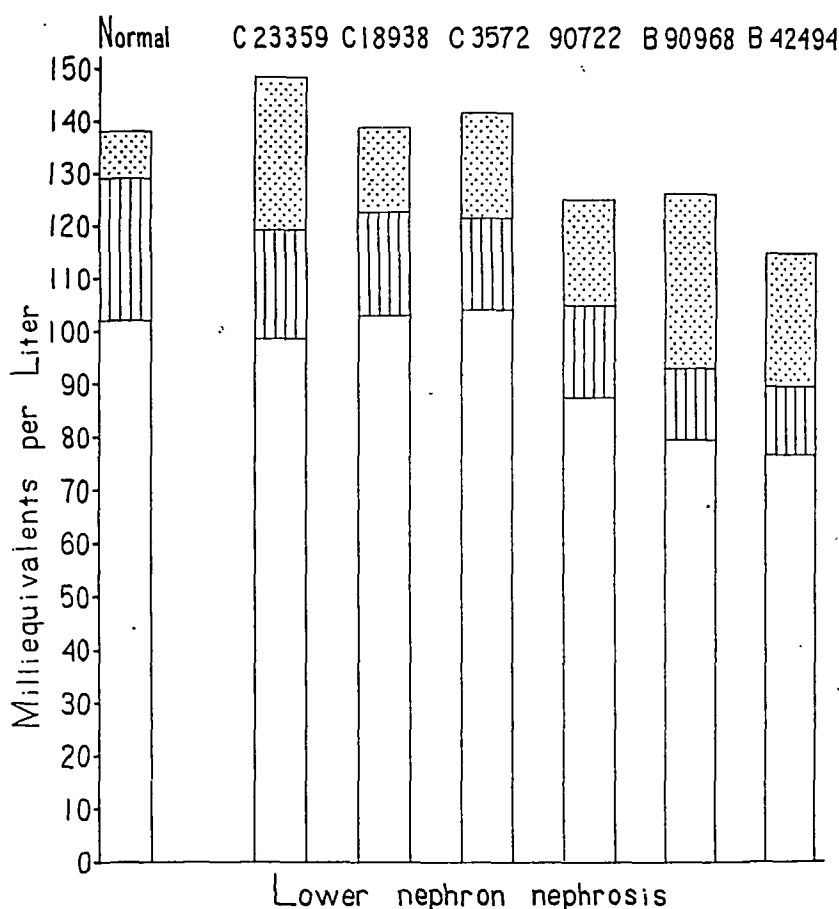


Figure 5—Electrolyte patterns of sera in patients with anuria.

turbances encountered in an active clinic. The reasons for this are several: 1. Sodium is an essential commodity which must be derived from the environment. It is not, however, a natural constituent of vegetable foods and occurs in relatively low concentration in meats and other animal foods. For an adequate supply of sodium reliance is placed on sodium chloride added to food, either in preparation or at the table, or both. When patients are given nutritive liquids or limited diets, care is not always taken to assure an adequate intake of salt. 2. Both sweat and gastrointestinal contents contain sodium. In their excretion of salt the sweat glands are only slightly, the alimentary secretory organs not at all, heedful of the need for or supply of sodium in the body. Profuse sweating, vomiting or diarrhea, therefore, withdraw

sodium salts from the body. Frequently this process is abetted by the unnecessary use of lavage with the aid of various tubes and suction devices by the physician or surgeon. 3. In certain types of disorders the kidneys lose their capacity to protect the salt supplies of the body, which they usually do with the greatest precision. Loss of the ability to reabsorb salt efficiently is one of the characteristics of renal insufficiency, including lower nephron nephrosis. In the presence of this defect sodium chloride and bicarbonate continue to appear in the urine when their concentrations in the serum have fallen far below the normal level. In Addison's disease, also, sodium is wasted through the kidneys. Two other conditions are recognized in which the power of the kidneys to conserve sodium salts is compromised: certain types of intracranial lesions and advanced pulmonary disease, especially tuberculosis. The last is of some importance because, occurring in patients who may be suspected of Addison's disease, it may confuse the diagnosis. There is not time at my disposal to discuss in detail this bizarre disorder to which we have recently devoted much attention. I might say that it should not be confused with the reduction of chloride seen in asthma, emphysema and other conditions in which chloride is depressed by accumulation of CO_2 in the blood. 4. Finally, a certain fear has been engendered in both the lay public and the medical profession of giving salt to sick persons, lest it precipitate circulatory failure.

Sodium deficiency has been defined thus far only in terms of the concentration of sodium salts in the serum and extracellular fluid because it is this concentration that controls the load of water in cells and the responses of the kidney. These organs display no concern about the edema of a thrombophlebitic leg so long as it keeps its place. Though edema may be uncomfortable, unsightly and even embarrassing, it is tolerated by the kidneys so long as it is attended by no disorder of the circulation or the composition of the serum that brings it to the attention of the kidneys. From the standpoint of overall exchanges of salt and of therapy, however, it makes all the difference in the world. The actual amount of sodium in the extracellular fluid is measured by the product of concentration and volume. It is perfectly possible to have a sodium deficit, so far as concentration is concerned, with an excessive amount of sodium in the body, if there is at the same time a greater excess of water. Vice versa, a salt-depleted person may have an abnormally high concentration of sodium in the serum if he is suffi-

ciently dehydrated. It is the incidence and treatment of these two types of states that I particularly want to stress. I shall use for illustration gastrointestinal disorders, reminding you at the same time that profuse sweating or wastage of salt through the kidneys will have an identical effect.

The normal person loses daily about a liter of water without salt by evaporation through the skin and respiratory system. (If, by reason of high environmental or body activity, he sweats, these losses will be much larger and will carry with them salt, but this we shall neglect for the moment.) If the non-sweating individual receives no water in any form, the sodium in his serum will become concentrated because of the loss of insensible perspiration. This is countered at first by the excretion of some salt in the urine. But after a time this stops and the sodium of the serum rises. It seems a paradox that reabsorption of salt should increase when the concentration of sodium in the serum rises; but when there is a deficiency of water this reaction serves a most useful purpose. Every increment of salt in the urine requires for its excretion a certain amount of water. By reabsorbing salt, therefore, the kidneys can save water. But there is a secondary effect that is equally important. As the concentration of sodium in the extracellular fluid rises, the osmotic pressure of that fluid also rises. This causes fluid to be drawn out of the cells. The cells thereby share in the loss of water, protecting the extracellular fluid from extinction. An excessive concentration of sodium in the serum is usually *ipso facto* evidence of dehydration.

The gastrointestinal secretions, with some variations of pattern that may be neglected for our purposes, are isotonic salt solutions, and all fluids introduced into the alimentary canal become isotonic solutions in the process of absorption. If, then, a person receiving no fluids loses by vomiting, diarrhea, fistulae or suction, gastrointestinal secretions or digestive juices, sodium salts and water will be withdrawn in proportional quantities from the extracellular fluid. Of itself this should reduce the volume of fluid in the body without altering the concentration of sodium in that fluid. While this isotonic fluid is withdrawn through the gut, however, the lungs and skin continue to eliminate water alone or hypotonic sweat. Consequently, overall more water than salt is sacrificed and the sodium concentration of the serum rises. Losses of gastrointestinal fluids, if not replaced by any means, cause an accelerated dehydration reaction with elevated serum sodium. Excessive sweating

has the same effect. Confronted with such a picture, the natural reaction is to give only glucose solution in order to lower the concentration of sodium. This is not, however, sufficient. Water or its equivalent may be given to dilute the fluids already in the body, but saline must be given in addition to allow for additional expansion. This subject did lose salt, only he lost proportionally more water. If all the fluid lost is replaced by water—or its parenteral equivalent, glucose solution—this will become at once evident. The concentration of sodium in the serum will fall below normal and the subject will develop stoker's cramps or miner's colic.

In vomiting and diarrhea this picture of dehydration with high sodium is seldom encountered because such patients take or are given water by mouth. Salt is poured into this water by the gut and digestive glands, which are stimulated to secretion by its presence. The consequence is that more salt than water is lost from the body and the concentration of sodium in the serum falls. The proportion of salt lost depends on the amount of water introduced, the length of time it remains in the alimentary canal and the volume that is lost by vomiting or diarrhea or removed by tube. If lavage is practiced, normal saline or slightly hypotonic saline brought to isotonicity with glucose should be used, because such a solution will provoke minimal secretion. It is far better, in the face of intractable vomiting, to give no fluid at all by mouth, relying for the moment on parenteral fluids. If water alone is used, since salt is lost in excess of water in vomitus or lavage fluids, replacement by glucose solution will aggravate the condition grievously. Even normal saline parenterally is inadequate for replacement, because it provides water and salt in equivalent proportions. Attempts to raise the concentration of sodium in the serum by means of normal saline solution will provoke edema with sodium deficiency. In this case the total amount of sodium in the body may be excessive, but its concentration in serum and extracellular fluids is below normal. This causes the cells of the body to become swollen and water-logged. Circulation and renal function fail. This is the condition in which patients with gastrointestinal obstruction or lower nephron nephrosis so often present themselves. The first indication is obviously to arrest the losses of salt by forbidding all oral fluids. It then remains to restore the proper concentration of sodium and the volume of fluid in the body. To achieve this end it has been proposed that all salt be withheld and that only

enough glucose solution be given daily to prevent ketosis and excessive destruction of protein. It is left to the kidneys to make the necessary adjustment by excreting water without salt. Since, however, the necessary amount of glucose—let us say 100 gm.—can not be given without enough water, 1000 cc., to replace that lost by insensible perspiration, this is at best a tedious process. Moreover, until it is completed, circulatory and renal insufficiency will persist. I agree heartily that normal salt solution under such circumstances is contraindicated. Normal saline should be used only to make up the volume of fluid in the body when this is deficient. Normal saline with glucose dissolved in it can also be used to restore the concentration of sodium when the volume of fluid in the body is normal or reduced. In this case insensible perspiration will aid in the adjustment. But to wait on insensible perspiration when there is an excess of fluid in the body seems overcomplacent. The most logical treatment in this condition is the administration intravenously of hypertonic salt solution. A liter of normal saline contains only enough sodium to take care of the liter of water it adds to the body; 300 cc. of 3 per cent sodium chloride, besides providing the salt required for its own volume, contains enough in addition to raise the concentration of 11 additional liters 10 milliequivalents; 500 cc. of a 3 per cent solution will provide 10 milliequivalents for 18 liters; 300 cc. of a 5 per cent solution will do the same for 21 liters. Such solutions, especially the 3 per cent, are well tolerated. Their administration under the circumstances that I have defined does not provoke heart failure and aggravate edema. On the contrary, it is followed by improvement of the circulation and diuresis. What I want to emphasize, however, is the general principle that in the administration of fluids both volume and composition must be evaluated and taken into consideration. Isotonic salt solution and 5 or 10 per cent glucose solution are not the only available instruments for the replacement of body fluids.

It has become increasingly evident that sodium, water and glucose are not the only objects of concern. Disturbances of the concentration of potassium, especially deficiencies of this element, are being reported with increasing frequency. The concentration of potassium in normal serum varies from 3.1 to 5.3 milliequivalents per liter (12 to 20 mg. per cent). If it falls below 2.0 or rises above 7.0 milliequivalents, definite disorders appear. The most serious of these involve the action of the heart and may be detected by means of the electrocardiograph. I shall

not describe these changes now; they have been well defined in the recent literature. It has been suggested that they be used instead of chemical analyses to detect disturbances of serum potassium and as checks on the effects of therapy. Although electrocardiography may be a useful adjunct to chemical analyses for this purpose, it is not an altogether satisfactory substitute. The electrocardiographic disorders, unless they are permitted to run their whole gamut, which is obviously undesirable, are not sufficiently specific to be regarded as pathognomonic. Other symptoms and signs that have been described are even less reliable. Weakness, sometimes approaching paralysis, has been described as a symptom of both hyper- and hypokalemia.

Provided that a person is receiving and absorbing food, a deficiency of potassium is unlikely to develop because potassium is such a ubiquitous component of foods. The subject who is not receiving or absorbing a diet, however, is deprived of this essential element. So long as the function of the kidneys is unimpaired, these organs protect the body most effectively against depletion of sodium, but potassium they conserve with far less efficiency. In the presence of a sodium deficiency, if the kidneys are intact, sodium may be so completely reabsorbed in the tubules of the kidney that only minute traces of the element appear in the urine; a urine free from potassium, on the other hand, has never been described. Potassium exists chiefly in the cells of the body to which it gains access and from which it is discharged, not by a simple process of diffusion, but in connection with metabolic reactions. If, then, potassium leaks from the extracellular fluid into the urine, the cells do not ordinarily replace it completely. In the absence of an exogenous supply of potassium in the form of food, serum potassium does not usually fall to a serious extent because cellular tissue, especially protein, is broken down and with its destruction potassium is released. Gastrointestinal secretions, however, also contain potassium, in concentrations distinctly higher than those found in serum. This element is, therefore, sacrificed in vomitus, diarrhea, fistulae, and when lavage is practiced. This constitutes another contraindication to suction and lavage. There can be no doubt that potassium deficiency of a serious degree has been and is still occurring with great frequency on the surgical services of our hospitals because of failure to recognize these fundamental facts. A very special case of potassium wastage attends the use of desoxycorticosterone. This steroid specifically promotes excretion of potassium.

Patients treated with desoxycorticosterone are, therefore, always in a somewhat precarious state with respect to potassium. So long as they eat and retain their food, they are protected. But, if, because of intercurrent illness or from any other cause, they fail to eat or develop vomiting or diarrhea, their serum potassiums may fall rapidly to dangerous levels.

Excesses of potassium in the serum are less to be feared. The condition in which they are most to be feared are states of extreme renal failure, especially anuria. Even when there is complete anuria, however, serum potassium seldom rises to dangerous concentrations if the composition and volume of the fluids in the body are properly preserved. It is difficult to raise the concentration of potassium in the serum of a normal animal to toxic levels with injections of potassium salts, not only because the potassium is promptly excreted by the kidneys, but also because it is absorbed by the cells. Even if the kidneys are removed, the tolerance for potassium remains quite high because of this protective activity of the cells. If a normal animal is deprived of protein, both nitrogen and potassium are excreted in rather uniform proportions as a result of the destruction of cellular protein. But if an anuric animal is subjected to the same treatment, under proper conditions, nonprotein nitrogen accumulates in the blood serum far more rapidly than potassium does. The potassium is retained in the cells. This power of the cells to take up and retain potassium constitutes an automatic protection against potassium poisoning. Of course there is a limit to this protection and it is not well to tempt nature too far by adding to the endogenous potassium when there is anuria or extreme oliguria. The patient with extreme oliguria or anuria should not receive food containing potassium, which excludes almost all natural nutritive materials. Carbohydrate should, however, be given in sufficient quantities, properly distributed, to maintain continuous carbohydrate combustion. This has a double beneficial effect. It minimizes the destruction of protein and promotes the retention of potassium by the cells, because the segregation of potassium in cells seems to be linked with utilization of carbohydrate.

This is most vividly illustrated in diabetic acidosis. At the height of this condition, when carbohydrate combustion is reduced to a minimum and renal function, owing to dehydration and circulatory collapse, is greatly impaired, potassium in the serum is usually elevated, sometimes to dangerous concentrations. When combustion of carbohydrate is

restored by insulin and glucose, and renal function repaired by administration of fluid and salt, serum potassium falls rapidly, sometimes to equally dangerous concentrations. This drop is the result of three processes: excretion by the kidneys, dilution by expansion of the body fluids, and movement into the cells under the impulse of the resumption of carbohydrate combustion. If, at this time, the patient can and does take food and fluids by mouth, these will provide protective quantities of potassium. If he can not, potassium must be given. It is, however, essential to know whether potassium has fallen before administering it. It would be a fatal error to give potassium in the early stage while its concentration in the serum is still elevated. Potassium chloride or a neutral solution of potassium phosphate may be given slowly intravenously. For this purpose it is our custom to dissolve about 100 milliequivalents of potassium (7.5 gm. of potassium chloride) in 500 cc. of distilled water. This can be diluted with from 500 cc. to a liter of normal saline or glucose solution. It may be necessary to repeat this dose.

It is evident from what has been said that, although the proper sphere of action of potassium is within the cells, where it must serve specific functions, effects of either deficiency or excess become apparent only when its concentration in the serum and extracellular fluids is altered. The load of potassium in cells can be varied within wide limits without recognizable response, so long as its concentration in the serum is normal. The most striking illustration of this is the syndrome of familial periodic paralysis. During the paralytic attacks, potassium is transferred, presumably by reason of some metabolic disorder, from the extracellular fluid into the cells, causing serum potassium to fall. If extra potassium is given, it may be taken up by the cells in the same way. There is, therefore, an overload of potassium in the cells. Nevertheless, the reactions of the patient, including electrocardiographic changes, are those characteristic of potassium deficiency.

This has been no organized analysis of electrolyte and water metabolism; but a rather hurried sketch of certain types of disturbances. My purpose has been to show that modern diagnosis and therapy by the aid of chemistry require more careful analysis of clinical disorders and more carefully considered individualized treatment. Knowledge and technical aids are available; it is time they were more widely and wisely utilized in the clinic.

THE PRESENT STATUS OF CLINICAL ELECTROENCEPHALOGRAPHY*

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THE clinical investigator has found in electroencephalography a powerful tool with which to attack some of the most baffling of the problems of nervous and mental disease. It is the purpose of the present report to summarize certain recent advances and to indicate what use can now be made of the electroencephalogram in practical clinical studies.

Before proceeding to this task, honor should be paid to those who pioneered. It was, of course, Hans Berger who pointed the way.¹ He showed that the electroencephalogram is surprisingly easy to record, but more importantly that it changes with age, with attention and with states of impaired consciousness. Credit should go to Fischer² who showed that abnormal cortical potentials appear during convulsions, and to Tönnies who demonstrated the practicability of ink-writing electroencephalographs,³ and to Albert Grass, who provided superb equipment for electroencephalographers throughout the world.⁴ The contributions of Kornmüller,⁵ Grey Walter,⁶ Adrian,⁷ Bremer,⁸ Jasper⁹ and others¹⁰ gave basic information and orientation to all early investigators.

In the past 30 years practically every normal and abnormal state of central nervous function in man and animals has been surveyed electroencephalographically. Tens of thousands of men, women and children have been studied with multi-channel equipment. Thousands of miles of records have been inspected and correlated with various clinical conditions. This work has placed electroencephalographic diagnosis on a solid statistical basis, but it has done more than that; it has made the electroencephalographer familiar with his instrument and his material so that he can look through the electroencephalogram at the

* Presented October 20, 1949 before the 22nd Graduate Fortnight of The New York Academy of Medicine.

brain.* In this respect he is like the roentgenologist who looks not at the grains of emulsion on the X-ray film, but at the picture of body structures. The electroencephalographer sees the 400 feet of paper with six or eight wiggly lines on it that forms the electroencephalogram, not in terms of its primary aspects but in terms of its neurophysiological and clinical correlates. Five sets of data have shown important correlations with the electroencephalogram: 1) brain metabolism; 2) age; 3) the level of consciousness; 4) the clinical symptomatology of epilepsy and related brain disorder (trauma, encephalitis, vascular disease, etc.); 5) the pharmacological action of stimulants, sedative and anti-epileptic substances.

The electroencephalogram gives evidence of a type of activity which must be described in general terms because, though it is found more highly developed in nerve cells than in the other tissues, it is nevertheless characteristic of protoplasm in general. It has been termed irritability; the tendency to release stored energy after thermal, chemical, mechanical or electrical stimulation. Voltage production is one form of energy release.

A tendency to rhythmic electrical activity is inherent in all neurone aggregates (ganglia, cord and brain). The cortex shows electrical pulsations with a voltage of approximately 5-500 microvolts and a frequency of 1-50 cycles per second. The primary sources of energy for the fluctuating voltage are glucose and oxygen. To use a mechanical analogy, these two substances are the mainspring of the oscillator, but the escape-ment or control of energy release lies elsewhere: in CO₂ tension¹¹ and in as yet unknown enzymes and neuronal mechanisms. Obviously any tissue which has as a major characteristic the release of energy must be provided also with mechanisms for storing energy and regulating its release. Although these mechanisms are not yet understood their operation is manifest in the electroencephalogram, for here one sees energy (derived primarily from the blood stream) transferred to the nervous

* Persons professionally interested in electroencephalography are now organized in many countries. The names, secretaries, and number of members of some of these societies are as follows:

English—The Electroencephalographic Society, Great Britain, W. Grey Walter, M.D., Secretary, Burden Neurological Institute, Bristol, England. 72 members.

French—Société D'EEG et des Sciences Connexes à Langue Française, Henri Gastaut, M.D., Secretary, 149 Promenade de la Corniche, Marseille, France. 50 members.

Italian—Italian Electroencephalographic Society, G. Moruzzi, M.D., Secretary, University of Pisa, Pisa, Italy. 30 members.

American—American Electroencephalographic Society, Dr. Robert Schwab, Secretary, Massachusetts General Hospital, Boston 14, Massachusetts. 107 members.

These societies have united to publish "Electroencephalography and Clinical Neurophysiology, an International Journal." Dr. Herbert Jasper, Neurological Institute, Montreal, Canada, is Editor-in-Chief.

system in finely graded quantities and channeled through neuronal pathways in a precisely regulated manner. This regulation of energy release is of extreme importance for proper function. Modulation or control of energy release in the nervous system is of two types: In the nerve fibers where conduction is the primary function, amplitude is held relatively constant and frequency is modulated (as is conventional in radio communication whenever interference must be kept to a minimum), but in synaptic areas (near the cell body) where interference, interaction and mixing are essential to normal function, amplitude modulation is combined with frequency modulation.

If more than the usual amount of energy is released, as evidenced by increased voltage production per unit time, clinical signs of hyperactivity appear. If less than the usual amount of energy is released, as evidenced by a decrease in the voltage production per unit time, clinical signs of depression of neuronal function appear. The specific symptoms that develop depend on the function subserved by the structures involved in the abnormal energy release. Thus it can be said that the general character of the dysfunction (hyper or hypo) and its time course are electro-chemically determined, but the specific symptom is anatomically determined.

Electroencephalographic patterns have their simplest form and the electrical sign (negativity or positivity) is most easily interpreted when voltage readings from points on the scalp (or some part of the brain) are referred to a relatively inactive reference point (usually the ear lobe). This has been called "monopolar recording." The term is inappropriate, however, because recording with one electrode is impossible. The term "bi-polar" has been applied to recordings from serial pairs of electrodes arranged in the form of a triangle or a line, the activity of each pair being referred back or forward to the next pair. The final description of voltage conditions in the brain will be the same whether activity is recorded with a common reference or with a series of references.

When the electrical activity of the brain is recorded between two electrodes A and B on the head, the possibility arises that both are active and that the resultant tracing is the algebraic sum of the two activities. "Bi-polar" recording tries to subtract from the sum of the activity at A and B other sums obtained by using A and B in conjunction with other points, thus arriving at an evaluation of the voltage con-

ditions at A and B. When a common reference is used the "stigmatic" electrodes are placed at A and B and any difference between the activity recorded is attributable to differences in voltage at A and B, the points in question; thus also for activity recorded from all other points to the common reference. In some cases, however, universal activity may be registered which may be due to activity at the reference point. This may be checked by moving to another reference. However, the same difficulty may arise with the new reference. By removing the reference point further away from the presumed voltage source, shunting is obtained which will tend to reduce the pick-up of activity. For most purposes the ear lobes are sufficiently removed from the brain to serve as satisfactory reference points. However, the anterior temporal spike focus of psychomotor epilepsy, which will be discussed later, usually spreads to the ear, and slow activity is also commonly recorded from the ear in cases with a tumor of the temporal lobe. The opposite ear may be used as reference in such cases or the vertex or occipital region may provide a satisfactory "quiet" reference, or recourse may be had to electrodes on the nose or on the chin. In order to get well away from the brain it may be desirable to place electrodes on the chest and use these as a reference.¹² The complication introduced by the electrocardiogram can be avoided if electrodes are placed symmetrically on opposite sides of the heart and interconnected through a potentiometer. Rather than pick up the full voltage of the heart it is desirable to keep somewhat away from it, and the positions ordinarily chosen for chest electrodes are the spine of the first thoracic vertebra and the right sterno-clavicular junction.

From animal experiments¹³ and from recordings in the depths of the human brain¹⁴ a negative voltage (referred to a relatively inactive reference) indicates that the electrode is in or on the discharging area. A positive discharge indicates that the electrode is beyond the discharging area.

Excessive thermal, mechanical, chemical or electrical stimulation slows, decreases and finally abolishes cortical voltage production.¹⁵ Thus, flattening of the electroencephalogram and disappearance of the brain waves can be considered an extreme form of slowing.* Depression

* A decrease in amplitude to the point of flattening is rarely encountered clinically. It is an extreme change which carries with it an immediate danger of death. A depression of amplitude resulting in an asymmetry of voltage production from homologous areas in the two hemispheres is a sign of minimal damage and has some clinical localizing value.

of voltage production (slowing or flattening) is a *primary* reaction to injury. In some cases, after mild depression of voltage production or during the phase of recovery from severe depression, a secondary disturbance develops; it consists of paroxysmal *excessive* voltage production. As indicated by the sudden failure of cortical function when the blood supply is cut off, the normal energy consumption of the brain is almost identical with the rate at which it is supplied. Therefore, abnormally great release of energy in the cortex is quickly limited by failure of energy supplies and followed by diminution or absence of voltage production. Excessive voltage production tends to spread, however, and to drive neighboring and connected neurones into similar activity. The greater the excess of voltage the greater the spread and the less precisely the voltage is held within the usual neuronal channels. This reaction of paroxysmal excessive voltage production is an irritative reaction to injury; it constitutes the pathological, physiological basis of epilepsy.

From the electroencephalographic point of view, epilepsy is a disorder of rate regulation which manifests itself as a tendency to abnormally violent and extensive discharge, i.e., as a failure to provide proper spacial and temporal limitation of voltage production. This failure of rate regulation is produced by the same agents which produce normal alterations of rate regulation, mechanical, thermal, electrical or chemical stimulation, but these must surpass certain physiological limits of intensity and duration. Epilepsy can be considered a "tumor of function;" a distortion of one of the chief normal functions of neurone aggregates (i.e., voltage production). Just as a true tumor can be considered a disturbance of temporal and spacial regulation of the rate of reproduction (a feebly represented function in neurones) so an epileptic seizure can be regarded as a failure of the temporal and spacial regulation of energy release. In this view epilepsy is not a disease, but a type of dysfunction. It can have no single etiology and will have as varied a symptomatology as the nervous system has specific receptor, effector and integrator functions. It will certainly be caused by many types of injury and almost any type of injury will be found in some cases to be imitated by a genetic defect.

In epilepsy three general types of abnormal voltage production are encountered. They are referred to as seizure patterns.¹⁶ The first is a discharge of unusually fast waves of increasing amplitude followed by interrupted fast waves and later by slow activity. This is the classical

tonic-clonic or grand mal type of seizure discharge (Fig. 1). If the entire brain is involved maximal neuronal activity becomes manifest in generalized muscular contractions and complete loss of consciousness. From the point of view of energy consumption it represents a super-maximal discharge which cuts deeply into the energy reserves and requires a relatively long period of recovery (stupor) before normal voltage production returns. The second type of discharge is the spike-and-wave pattern which appears in its most perfect form as the three-per-second wave-and-spike of petit mal epilepsy (Fig. 1). In this type of discharge each spike of excessive voltage production is followed by a third-of-a-second of stupor (the slow wave) which apparently allows for recovery of function and the possibility of another discharge. However, as the pattern continues the spike usually tends to drop in voltage and the frequency of the repetitive pattern tends to slow from an initial approximately four-per-second to a final two-per-second rhythm. This type of discharge is rarely followed by stupor; it is a relatively conservative paroxysmal dysrhythmia, and is less disorganizing to central nervous function than the grand mal type of discharge. It is associated with three-per-second clonic movements of the head and eyes, posture is usually maintained, and consciousness is commonly diminished but not completely lost. The third type of seizure pattern consists of high-voltage six-per-second and square or saw-toothed four-per-second waves. This type of discharge is referred to as a psychomotor discharge (Fig. 1). It is associated with mental confusion and poorly coordinated but apparently purposeful movements. It is rarely followed by stupor. The psychomotor pattern is the one which is the most nearly normal of the three chief types of seizure discharge. Further study has shown that it is associated with a focus of negative single spike-seizure activity in the anterior temporal region.¹⁷

A single spike (Fig. 1) is the minimal epileptic discharge; it is commonly asymptomatic, and commonly focal. Spike foci can occur anywhere in the cortex, but they are particularly common in the anterior temporal region. A spike focus in the anterior temporal region has been called a psychomotor type of focus because it is usually associated with psychomotor seizures (trance-like attacks and confusional episodes). The extreme commonness of a focus of spike-seizure activity in the anterior temporal region suggests that this is the most vulnerable of all cortical areas to the irritative type of injury which underlies epilepsy.¹⁸

the depths of the brain. The frequency of 14 and 6 per second suggests that they arise in the thalamus where potentials of this general frequency have been localized by Morison et al²⁵ in the general region of the internal medullary lamina. Such discharges are usually associated with a history of "fainting spells" and a variety of symptoms suggesting thalamic disturbances.

A report in preparation²⁶ will deal in detail with exceedingly fast non-paroxysmal activity (35-40 per second) (Fig. 1, F-3) which appears best in the precentral regions during light sleep. This, like very fast activity (Fig. 1, F-2), correlates with epilepsy and related organic brain disorder, but it is commonly associated with personality disturbances and is particularly common in post-traumatic psychosis.

By regarding focal evidence of primary and secondary reactions to injury the informed electroencephalographer with adequate equipment is able in many instances to localize lesions which are not apparent from neurologic or roentgenographic examination. Thus, the modern neurosurgeon or neurologist finds the electroencephalograph indispensable. He will not be surprised or too disappointed by cases in which a huge atrophy or widespread demyelination shows little or nothing in the electroencephalogram, for destruction of neural elements does not show well in the electroencephalogram; absence of activity is by no means as evident as disordered activity. An inflammatory process, like acute encephalitis, tends to give maximal electroencephalographic findings even in cases where there are minimal clinical signs, and this helps to distinguish it from a more chronic disorder, for example, multiple sclerosis where the electroencephalographic findings are usually slight compared with the clinical signs. Likewise, a small metastatic carcinoma in the cerebral cortex, because of its rapid growth, usually produces more electroencephalographic disorder than a huge but slow-growing meningioma. If electroencephalography is to be used successfully by the clinician he must familiarize himself with it and realize that the electroencephalograph shows functional rather than structural disorder. The severest electroencephalographic disturbances, for example, convulsions and stupor, are not usually associated with demonstrable structural change. A violently discharging epileptic focus, when identified at operation by direct recording from the cortex, and when ablated by the neurosurgeon, commonly appears normal to microscopic examination.²⁷

Although electroencephalography is of value as a supplementary aid

to classical neurology and neurosurgery, which subjects deal with gross or microscopic evidence of structural changes (pathological anatomy), it does something more, something new. Although it does not correlate well with anatomical changes and signs of structural deficits which are essentially irreversible, it does correlate with pathological-physiologic changes which are reversible and amenable to medical and surgical therapy. It opens a new field of dynamic neurology and physiological psychiatry. Hans Berger would be happy to see how his brain child has prospered.

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A CHRONICLE OF ONE HUNDRED YEARS OF OTOLARYNGOLOGY*

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To recount a century of otolaryngological achievements is to undertake a task of great magnitude and responsibility. An initial inquiry into the progress of otolaryngology during the past one hundred years reveals an extreme breadth of material that deluges any attempt at selection and baffles the preparation of a readable and coherent text. It is amazing to note the accumulation of bibliographic data of professional significance deposited within our otolaryngological storehouse during the past century. Obviously I cannot remove all of them, classify them specifically and work them into something of tangible educational value for practical usage. I can only hope to touch the high spots of one hundred years of advance, not in the form of a catalogue but more as a record in abstract of those accomplishments with which I can claim some personal experience.

An awareness of the impact of contemporaneous developments in medicine outside the field of pure otolaryngological discovery is a responsibility that must be faced in treating this subject. The science of otolaryngology has not grown and developed as an entity distinct and separate from the other sciences. To illustrate this point I need only mention the tremendous influence the discovery of the chemotherapeutic and antibiotic agents exerted upon otolaryngological diseases during the past decade. Sir Alexander Fleming's colossal discovery of the antibacterial effects of penicillin has revolutionized the practice of otolaryngology and altered it to such extremes that it now bears only a faint resemblance to its stature of a decade ago. Here we observe the tremendous effects of contemporary discovery. The acute infections of the pharynx, retropharyngeal abscess, peritonsillar abscess and the deep suppurations of the neck have nearly vanished. The acute inflammatory processes within the sinuses run a course of short duration and seldom

* Given before Centennial Meeting of The Section of Otolaryngology, April 16, 1947.

give rise to complications under the influence of the chemotherapeutic and antibiotic agents. The serious complications of mastoiditis which comprised a significantly important responsibility of otolaryngological practice and held the major interest of the members of our profession ten years ago are rarely in evidence today. The almost complete annihilation of temporal bone surgery and the marked decrease in the incidence of acute suppurative processes within the structures to which we give attention have prompted the statement many times in otolaryngological circles that otolaryngology has entered upon a period of decadence.

The future of otolaryngology is, however, by no means dark. There are great resources in this field which have not yet been tapped and these will be made available through scientific research. There are colossal opportunities for research in otolaryngology today, the promotion of which will open many new fields for practice. Consider if you will the unsolved problems of cancer, allergic reactions, nerve regeneration, the neurological manifestations of otolaryngological diseases, deafness and the rehabilitation of the hard of hearing; these and many others furnish innumerable investigative studies in which the joy of creativeness will be experienced by many of our colleagues and from which new methods of practice will be derived.

In the twenty year period from 1840 to 1860 there is little significant literature pertaining to the clinical aspects of the ears, nose and throat. Anatomical studies had been made but they were not correlated with clinical observations in any attempt to rationalize etiological influences and the behavior of disease. Isolated cases of epistaxis, sore throat and injuries to the ears and nose were described but records were brief and methods of treatment devoid of any vitality that would permit them to live beyond their time.

It must be acknowledged, however, that otorrhea was attracting the attention of some observers and exciting apprehension because of its potencies for serious complications. It was suspected at first that a discharge from the ear afforded "relief to some other local irritation." We find it stated that "in teething, ophthalmia, and other inflammations nature very commonly establishes this discharge which undoubtedly relieves these diseases." The evil consequences of chronic suppurative otitis media, namely, meningitis and brain abscess were becoming subjects of grave consideration. As one writer expresses, "the disease may

pass through the delicate organs of hearing, attack the membranes and even the substance of the brain producing then, and not till then, convulsions and death." One author recollects that "when a boy, in company with others, boys and men, a common amusement among them was to blow smoke from their segars they were using through their ears and a considerable percentage of these individuals in a country village could perform this feat."

While Phillip Bozzini, a German physician, announced in 1795 that he had conceived a means of performing endoscopy, he did not describe his endoscope until 1805. His invention received only scant attention and occasioned little interest until about forty years later when in 1843 an English surgeon, John Avery, described an instrument which visualized the vocal cords "better than it had ever been possible to see them before." Ten years later in 1853, Desormeau, a French physician in Paris, described an illuminated instrument of such practical value that historians have designated him the "Father of endoscopy." While the instruments and techniques for practical endoscopy upon living human subjects developed approximately one hundred years ago, the idea of examining the cavities of the body was posed some forty years before this period. It is another instance of one of the sad reproaches to the scientific world, namely, that many of our great discoveries go unnoticed and are lost to humanitarian service for many years after they have been made available to us. Sulfanilamide prepared in 1908 remained dusty on the organic chemists' shelves for a quarter of a century before it was recognized as a great savior of suffering and untold human lives. Similarly, penicillin was discovered in 1929, yet it remained obscure and attracted little attention until the pressure of demand was felt by the advent of World War II.

Mirror laryngoscopy was described in 1792 but the mirror as a diagnostic instrument was not employed to any great extent until its advantages were recommended by Czermak in 1858. Nearly ninety years have elapsed since this important but simple diagnostic procedure was recommended yet it is still neglected all too frequently by physicians in their routine daily practice. We continue to emphasize the great need of an early investigation of the causes of hoarseness, lesions which reveal their true identity in the vast majority of cases in the reflected image of the larynx in a mirror, yet hundreds of patients with operable carcinoma of the larynx come to grief yearly because of sheer neglect. It is another

instance of the obvious thing being the one most frequently overlooked.

In 1860 we begin to read an otolaryngological literature which departs from generalities and records something which is more concrete. Otolaryngologists began to focus their creative energy upon specific anatomical studies, etiology and the diagnostic signs and symptoms of disease. Joseph Gruber, Prussack, and Kessel studied the histology of the tympanic membrane, investigated its attachment to the handle of the malleus and the short process, and wrote in general on some anatomical considerations of the middle ear. These studies brought enlightenment to the clinical behavior of disease, and inspired reports of acute and chronic suppurative processes in the temporal bone, and functional disturbances of the auditory mechanism. The role of the eustachian tube in admitting infection from the nasopharynx to the tympanum was recognized. Politzer's air douche was recommended after perforation of the tympanic membrane had occurred.

While the otolaryngologists of this age were familiar with the etiology and symptomatology of acute suppurative processes in the temporal bone and aware of their complications, they were obviously woefully in the dark in a knowledge of adequate treatment. But they were not without their convictions. In their characteristically professional manner they write succinctly and without fear of derision concerning the specific virtues of "half moon blisters, applied behind the ears and, an ear lotion of four grains of the acetate of lead to an ounce of water instilled into the ear, the use of mild astringent gargles, fluid extract of sarsaparilla, a teaspoonful internally twice a day, exercise in moderation, and the avoidance of coffee and most of the unnecessary stimulents."

In the 1870's we note that the conservative treatment of acute otitis media versus paracentesis of the tympanic membrane is a controversial issue. The literature records a great deal of acrimonious dispute on this matter even to the extent of severe ridicule and bitter imputations for those who resort to surgical measures. One writer in 1876 lays great stress on careful cleansing of the ear with an alkaline solution but vigorously opposes the paracentesis. He calls it a "fashionable" operation and concludes by analogy that if no oculist would perform a paracentesis of the anterior chamber for the sake of removing pus, then why should we approve of a paracentesis of the drum cavity for an acute inflammatory process of the middle ear.

In the next five years, 1870 to 1875, we find that the paracentesis became a popular method of treatment for acute suppurative otitis media. Many cases of acute inflammation of the middle ear treated by puncture of the drum head are briefly recorded but otolaryngologists continued to feel their way carefully in the treatment of temporal bone infections because we note that when signs and symptoms of acute mastoiditis put in their appearance, surgical efforts consisted only of an incision made through the skin down to the mastoid about one inch in length, one-half an inch behind and parallel to the attachment of the auricle. Obviously such a procedure was helpful in those neglected cases where the infection had perforated the mastoid cortex and had become active under the periosteum of the mastoid process. From ignorance of surgical techniques and in part too from the lack of courage, operations for acute mastoiditis were limited to a soft tissue incision and drainage.

The surgeons were soon to become bolder, however, because in 1879 a successful operation for acute mastoiditis is reported by opening the cortex of the mastoid bone. Dr. A. G. Gerster, a surgeon at the German Hospital and Dispensary, New York City, stated that he was describing this case in the literature "to encourage others to prompt action in similar instances." The operator deprecated the use of such instruments as the trocar and trepan because they could not be kept under observation and were therefore unsafe. He reports that "the employment of the chisel and mallet seems to offer the greatest security. Several advantages will accrue if the action of the chisel is tangential to the surface of the cranium: First, the bone will be opened layer by layer and thus laceration of the transverse sinus be best avoided; secondly, the cavity of the abscess is converted into a shallow basin that will afford excellent drainage." Schwartze had previously perforated the mastoid process with a drill but because he had been repeatedly deluded in his expectation of finding pus, there were often indications for a more extensive excavation of the mastoid process with chisel and spoon. In nearly all instances, however, we find that an operation upon the mastoid process was delayed while conservative measures were employed, particularly the application of leeches to the edematous swollen mastoid region.

We find in the literature of this period an appreciation on the part of otolaryngologists of functional ear diseases. The profession is cau-

tioned about the possibility of psychic conditions being reflected in the form of pain to the region of the ear and a warning is sounded not to interfere surgically with these patients. We read that "if the patient bears his pain badly, suffers from great depression of spirit, dwells to an extreme upon his illness, and is generally so much taken up with the severity of his pain as to have room for nothing else, we should hesitate to perform a surgical operation no matter how trivial it may be." The author goes on to say further: "we have no right, I think, to perform operations to clear up doubtful diagnoses; if in case the operation proves to have been unnecessary, the patient will be decidedly the worse for it." His admonition is given pedagogical emphasis when he states that "in teaching medical students, I have always found them when fully awakened to the danger of neglecting certain diseases to be more apt to do too much than too little, especially with the knife and active drugs."

In the time that has passed until the present day the importance of this warning has become no less significant than when it was expressed in 1879. The unending moral obligation of the profession to avoid surgical measures for diagnostic purposes and in patients with obvious psychogenic disturbances continues, I fear, to be treated lightly in our present day. We have come a long way in the development of surgical judgment since the above quotation was written but there is more to be learned and moral assessments to be made if we are to rank highly in the judgment of our professional colleagues.

It must be recorded that in 1876 Hartman opened the mastoid process through the external auditory canal with a drill. This was an early demonstration of the end-aural approach. Schwartze spoke most sharply against this technique because, as he warned, we then "drill into the darkness." Its advocates countered, however, by reciting the time-honored axiom that "when we become well acquainted with the anatomical relations many things will be illuminated that are now dark to us."

In the early 80's we discover that the nose and throat are beginning to attract attention and that the otolaryngologists of the day are advocating operations for the removal of hypertrophied adenoids and tonsils and the relief of nasal obstruction. The galvanocautery is recommended for the reduction of hypertrophied tonsils. The tonsil was gradually burned until the remaining portion was on a level with the palatine

folds. One or two areas were cauterized at each sitting and usually only one tonsil was operated upon at a time. From twelve to thirty sittings were required to complete the process and operators freely admitted that they noticed a disagreeable odor from sloughs and an impairment of appetite in consequence of their surgical efforts.

Other members of the profession questioned the utility of the galvanocautery, emphasizing the difficulties in the case of a struggling child who could not be induced to have a second sitting after the first painful experience. The dangers of ether in the presence of the galvanocautery were recognized and local anesthesia had not yet received popular approbation by the profession. Tonsillotomy was favored by many operators. The proponents of this procedure agreed that if they removed a thin slice of the gland they did no good whatever; but on the other hand, if more were removed grave hemorrhage might occur. One author explains that "too often this fact is applied as a sop to the conscience of timid operators and as an excuse for an incomplete operation. We should come down to the level of the pillars of the fossae but on the other hand we should not enucleate. The operation should be done with the tonsillotome; with bistoury there is greater risk of hemorrhage."

The submucous resection of the septum was preceded by an incredible number of destructive intranasal procedures, turbinates were sacrificed, the galvanocautery was used with subsequent stenosis and a variety of crushing procedures recommended to straighten the septum. One wonders why the simple yet most widely employed and singularly successful intranasal operation, the submucous resection of the septum, remained undiscovered until the turn of the century. In a most comprehensive paper presented at the 56th Annual Session of the American Medical Association in 1905, Dr. Otto T. Freer described the operation for submucous resection of the septum. The pervasive popularity and use of this operation seem to have been established shortly after this date.

Total extirpation of the larynx must have been a futile and discouraging operation in this period (the 1880's). Patrick Heron Watson of Edinburgh was the first to demonstrate the practicability of the operation in 1866 by performing it upon a patient, although the result was fatal due to a postoperative pneumonia. In 1883 Dillroth performed the laryngectomy at Vienna in sufficient numbers and with a degree of success that might entitle him to the credit of having made the opera-

tion a feasible procedure. The statistics of this age on total extirpation of the larynx for malignant disease are appalling. A table published in the *Journal of Laryngology and Rhinology* in 1887 records 103 cases; 40 died from the immediate effects of the operation. Others succumbed from inanition, pericarditis, lung abscess and septicemia within a few months until in the end there is recorded in this series only 9 out of 103 patients living twelve months after the operation. But in spite of these grievous results, the laryngectomy had ardent supporters in the 1880's. Many from the ranks of our specialty continued to study this problem and strove diligently to solve it. They met the challenge and through unity of thought and agreement directed a non-emotional approach to the various phases of this affliction and eventually established practical surgical procedures for the eradication of malignancy of the larynx. When one is reminded that for nearly three-fourths of a century leading apostles of laryngology have directed opinions to the real issues of laryngeal malignancy and tackled the job of surgical intervention step by step to find a cure, he is skeptical of the claims of success today made by the x-ray therapist of limited experience in this field. Too frequently surgical measures are unnecessarily delayed in the hope that palliative procedures will eradicate the disease. X-ray therapy is useful but it bears a minor relation to that conviction which governs my principles of procedure, namely, the necessity of operative interference when the larynx is the seat of an operable cancer. I am unwilling to compromise with any other recommendation and I hold the opinion that in most instances it is the most charitable method of treatment in that it minimizes suffering and gives greater assurance of longer survival.

While ether and chloroform have been used for approximately fifty years; we find considerable acrimonious dispute in the early 1890's in regard to the comparative toxicity of these two agents. Many of the hospitals in this country, even the large institutions in metropolitan areas had failed to keep records so that it was exceedingly difficult to compile statistics on the comparative advantages or disadvantages of ether and chloroform. As late as 1890 opinions gained from meager experience gave rise to the statement in some quarters that ether and chloroform were equally safe. It was generally agreed, however, that more dangerous symptoms had occurred when chloroform was used and that this anesthetic should be employed "in strong patients or when brain and

kidney diseases were present." Ether was advocated for "weak persons" but hospital records seem to indicate that chloroform was the anesthetic usually selected, probably because of its rapid action and because of failure as yet to appreciate its dangers.

An important advance in otolaryngology was the recognition and treatment of septic thrombosis of the cranial sinuses, resulting from suppurative disease of the middle ear and mastoid. To Zausal of Prague must be given the credit for the first therapeutic recommendation in 1880. He performed a ligation of the internal jugular vein in 1884 but his patient did not survive. Horsley of London, quite unaware of any previous effort to accomplish this technique, ligated the jugular vein in 1888, but his patient also met a fatal termination. The same year, Lane of England and Hoffman of Germany repeated the procedure previously recommended and were rewarded by successful results in both patients. When in 1889 to 1890 Ballance of London reported four cases with two recoveries, the operation was enthusiastically received by the profession and became a universal procedure in all countries where modern medicine was practiced. In the years that followed until the advent of chemotherapy and the antibiotics, a controversial issue was whether the operation should be restricted to a simple removal of the septic thrombus from the sigmoid sinus or extended to include a ligation or even a resection of the internal jugular vein. As far as I am aware this dispute was never settled to the satisfaction of the otolaryngological profession. It has obviously ceased to be an issue, however, since the incidence of lateral sinus thrombosis is infrequent and specific therapeutic measures are at our disposal. Although some impressive anatomical studies have demonstrated that there is a dense venous drainage through the tributaries of the jugular bulb and vein, and for this reason there was justification for skepticism concerning the effectiveness of jugular vein ligation, the operation nevertheless was frequently followed by phenomenal improvement of the patient. It seemed to be another instance of a septic process failing to follow the course anticipated from a study of practical anatomical considerations.

With the turn of the century we note that otolaryngologists in this country were performing complete operations upon the nasal accessory sinuses and instituting those principles of sinus surgery which are recognized to be the accepted ones of today. The technique which they advocated called for the complete eradication of all the diseased

processes, the meticulous removal of the lining mucous membrane of the sinus whether it be the maxillary, ethmoid, frontal, or sphenoidal sinuses, and the obliteration or maintenance of permanent drainage of the sinus cavity. Modern surgery is making more skillful approaches to the sinuses, reducing deformities to the minimum, and embellishing the techniques in some of their minor aspects, nevertheless, in the early 1900's the fundamental principles of sinus surgery were as well recognized and executed as they are by the surgeons of today. When the otolaryngologist's ingenuity failed him and this seemed to have occurred many years ago in surgery of the nasal accessory sinuses, he turned to the adornment of technical methods. The latter enriches the beauty of technique and enhances the interest of operators of varying degrees of skill but the end results in terms of service to the patient have gained nothing that was not accomplished by the procedures advocated and performed four decades ago.

We might span the period of twenty years from 1910 to 1930 by a simple glossary of significant otolaryngological advances. At the beginning of this period the value of roentgenology in otolaryngology was called to the attention of the American specialists. It was emphasized that the roentgenological diagnosis of sinusitis was based on the principle that the rays "passing through a bony cavity filled with air give the contrasting outline which is sufficiently different from that obtained when the air is replaced by secretion or granulation tissue." The roentgenologist was warned, however, that he "should not be tempted too far beyond this basic fact in his diagnostic ardor." It was emphasized then, as it is today, that close collaboration between the otolaryngologist and the roentgenologist would be productive of mutual understanding and consequent effective service to the patient.

About this time we were urged to give serious consideration to the faucial tonsils as a gateway to general infection. It was felt that many general infections developed from acute and chronic inflammatory disease of the tonsils, and that tonsillectomy was indicated in pericarditis, myocarditis, endocarditis, arthritis, chorea, neuritis, pleurisy, tuberculosis, iritis, phlebitis, osteomyelitis, Hodgkin's disease and possibly certain forms of leukemia. The pendulum of enthusiasm obviously swung too far and it required years of observation and study to prove that all these infections could not be charged to a tonsillar origin. This wave of interest in tonsillar sepsis probably had its virtues, however,

in that it made the otolaryngological profession cognizant of the fact that the lymphoid tissue of the pharynx is sometimes the portal of entry for the infections which produce swollen joints and damage the heart and kidneys.

For many years indirect laryngoscopy had been advocated. Then in 1914 we were urged to use the direct method in that it was a practicable procedure for children, overcame the handicap of the reversal of the image in a mirror, and could be employed for operative procedures under general anesthesia.

The possibilities and limitations of suspension laryngoscopy were described in 1916. It found favor in many clinics because it immobilized the patient and allowed freedom of both hands of the operator. About this same time the guillotine for tonsillectomy was recommended because of its speed, better cosmetic results, less bleeding, performance by the sense of touch and its practicability under nitrous oxide anesthesia.

In 1917 otolaryngologists were becoming apprehensive about the development of acute pulmonary abscesses, occurring after operative procedures on the upper air tract. Numerous explanations for this grave complication were offered including hematogenous and lymphogenous spread of infection. It is a significant fact, however, that improved methods of anesthesia and adequate suction of the operative fields have greatly reduced the incidence of this hazard. Direct gravitation of infected material into the lower air passages must have been the responsible influence in most of these cases.

In the period from 1910 to 1930 I am impressed also by the fads and fancies in otolaryngology. Might it not be truthfully stated that the eye complications arising from diseases of the nasal accessory sinuses, particularly iritis, choroiditis, and retrobulbar optic neuritis were over emphasized? Did we not stress too radically the occurrence of sinusitis in infants and children and perform many unnecessary operations upon patients in the early years of their growth? Were we not led astray by the presumption that asthma was the result of a nasal reflex and that radical operations upon the nasal accessory sinuses for the removal of polypoid disease were curative measures? It is doubtful that there are any votaries of this theory today. Time and experience have obviously placed them in an ignominious position because the contentions of 1930 in regard to the relation of asthma and

chronic sinusitis have not been sustained. Convictions of the existence of a sphenopalatine ganglion syndrome were fleeting; early opinions on the advantages and disadvantages of the various local anesthetics in the nose and throat have not stood the test of clinical and pharmacological investigation, and the occurrence of deafness in patients with vitamin deficiencies has not been substantiated by scientific studies of an acceptable character. While these may have been some of the whims of the profession, they perhaps had their virtues in that they evoked academic interest and in some instances gave rise to theories which were reduced to facts for practical usage in otolaryngology.

To French radiologists belongs the credit of the first use of lipiodol and its introduction to roentgenologic practice. About 1927 the employment of a radiopaque substance in the visualization of the lower air passages was established in this country as an aid to the diagnosis of bronchial and pulmonary disease. It opened a wide field of study from both a diagnostic point of view and the teaching of practical anatomy.

In the literature of the 1920's we observe a growing interest in hay fever and the clinical manifestations of allergy. The cutaneous or scratch method of testing patients for pollen reactions was gaining favor and thorough surveys of botanical flora were being made at certain seasons of the year in many parts of the country. It was the beginning of a specialty in which reputations were to be made and yeoman service rendered to patients afflicted with a condition that heretofore had resisted all forms of local therapy.

In 1922 our attention was called to the disease agranulocytic angina although the etiological influences responsible for this condition were not understood. Attempts to find a specific organism invariably failed. The condition of the bone marrow, however, gave some evidence that the disease was probably due to a toxin that destroyed the granulocytic blood cells and inhibited the blood forming centers of the bone marrow. My memory is still vivid of several tragic cases seen on our wards about this time; patients with agranulocytic angina to whom repeated doses of pyramidon were administered for headache and general discomfort.

Until this period of the 1920's our popular text books had taught that primary carcinoma of the lung was exceedingly rare. Improved instruments and bronchoscopic technique were beginning to demon-

strate that this condition was by no means as rare as formerly stated. In the previous decade the diagnosis had been made at autopsy; now we were beginning to observe the true identity of the lesion through the bronchoscope. There seems little doubt now that we are experiencing an actual increase in malignancy of the lung and not a relative one due to more precise methods of diagnosis.

A better understanding of acute suppurations of the mediastinum and the procedure of cervical mediastinotomy greatly reduced the mortality from this disease in the late 1920's. In 1931 petrositis was revealed as an entity and understood both in regard to the pathology of spread of the infection and the technical procedures for adequate drainage. It should be regarded one of the great contributions to otology, a savior of suffering and lives from the period of the early 1930's to the advent of chemotherapy and the introduction of the antibiotics.

Although modern otolaryngology may be said to have antedated the advent of chemotherapy, it must be admitted that the introduction of the sulfonamides gave rise to a changed point of view in respect to the practice of our specialty. Proof of this fact was the often repeated statement by authorities that chapters in our text books would need to be rewritten. We observed an abrupt shift from discussions of inflammatory processes to such studies as the physiology of the nose, neurological lesions which influence the various senses, plastic surgery, the embryological derivations of tumors and cysts, and noteworthy investigations of disturbances of the auditory function and the facial nerves.

Important advances have been made within recent years in our understanding of Ménière's disease. We now recognize it to be a hydrops of the otic labyrinth, a condition which occasionally responds satisfactorily to different forms of medical therapy. No doubt, too, it is prone in some instances to undergo spontaneous intermissions or remissions. Surgical procedures upon the labyrinth, as for example, decompression and electrocoagulation, have given results of promise equal to those obtained from a subtotal section of the auditory nerve.

We have experienced two World Wars within the past one hundred years but a review of otolaryngological practice during both of them leaves one with the impression that noteworthy accomplishments were not conspicuous by their number. This is to be expected when one recalls that most otolaryngological staffs in various teaching centers

were greatly reduced by a call to military service and the personnel which remained in civilian practice were overwhelmed by routine responsibilities in the care of the sick. More significant perhaps is the fact that special emphasis was placed upon fields of research which did not fall within the province of otolaryngology. The war demanded that particular attention be given to investigations pertaining to the prevention and treatment of infectious diseases, the care of the wounded, psychiatric disturbances and physiologic problems which arose as the result of placing individuals in abnormal environments.

In spite of the rather undignified position our specialty assumed in military service and in spite of the fact that otolaryngologists in general were subordinated to other professional personnel in the army, the members of our profession saw their responsibilities and gave their unfailing support to the job at hand. One evidence of devotion was seen in aviation medicine. The influence of radium in the prevention and treatment of anomalies of pressure within the middle ear was well known prior to the war and it remained, therefore, for members of our specialty to recognize its indications and to employ it effectively in conditions occurring among aviation personnel.

Nerve grafting and nerve anastomosis attracted the interest of members of our profession and led to the development of surgical techniques more practicable in their application and productive of greater success than attained at any previous time. Men fundamentally trained in the anatomy and pathology of the temporal bone led the way to memorable progress in this field.

In the study of acoustic trauma, interesting advances were made during the war by representatives from our ranks. While injury to the auditory function did not become a problem of great magnitude, it must be granted that otolaryngologists were quick to respond to the request from military authorities for a better understanding of this condition.

I point with pride and with a deep sense of gratitude to those far-sighted and efficient otolaryngologists in military service who created an epochal program of service in the army and navy centers for the rehabilitation of the hard of hearing. They achieved phenomenal progress and rendered a service that will go down in history as one of the brilliant examples of humanitarian efficiency during the war. Advances among civic agencies are usually conspicuous by delay but I venture

the opinion that the impetus given this magnificent program of service to the hard-of-hearing by military personnel is destined to inspire, if not demand, a similar plan of action in civilian life.

It is encouraging to observe within the past decade that our profession is endeavoring to offer something more to the public than elaborate programs of prevention and expansive statistical compilations in the field of impaired hearing. Otolaryngologists and workers in the acoustic sciences are now wisely directing attention to the significant problems of deafness and formulating programs of therapy which give promise of real service to the hard-of-hearing. Thanks to recent studies, otolaryngologists are now equipped with the means of producing an atrophy and retrogression of lymphoid tissue responsible for anomalies of pressure within the middle ear. The use of radium in this type of deafness is an epoch in the progress of therapy and gives hope of saving or restoring serviceable hearing to children in whom the pathological changes in the tympanum are due to an occlusion of the eustachian tubes by lymphoid tissue.

There is justification it seems to me for the present widespread interest in the surgical treatment of otosclerosis. The one stage operation stands today as the only therapeutic measure which has been of service to patients with this disease. The fenestration operation constitutes a magnificent contribution to this field, not only because it has given serviceable hearing to some of the unfortunate victims of otosclerosis, but for the reason too, that it has inspired a deeper interest in the anatomy of the temporal bone and brought together some sincere and intelligent persons from the ranks of the medical sciences to study this problem and find its solution. From this operation, observations have been made and theories have been derived. There is a good chance that by further careful experimentation some of these theories will be reduced to facts.

I cannot pass by without mention the noteworthy progress our specialty has made in the training of young men in otolaryngology. Education above the level of undergraduate studies is not only a mark of the medical profession but a significant requirement that has assumed increasing importance with the evolution of American medicine. Its progress has not been rapid nor has it yet achieved exemplary objectives, nevertheless, it has developed resolutely into an essential program that demands the attention of all graduates of medicine today.

Most of us can remember that less than three decades ago the general rotation internship was not considered essential to the practice of medicine, nor was it required by our State Boards of Registration for licensure. Today no young graduate would attempt medical practice without at least one year of internship, nor would the young doctor venture to apply for the study of a specialty without completing the intern year because he knows that this requirement is imposed by all reputable graduate medical schools and departments in this country. Thus we find that the rapid progress which medicine has made in recent years, particularly its advances in the field of specialization, has initiated a public demand for technical skills and specialized capabilities that can be furnished only by the individual who keeps in stride with continuing education throughout his lifetime of useful service.

One of our greatest advances in the education of the otolaryngologist has been the establishment of curricula of continuing study which offer training to staff members for a three, four, or even five year period. In these groups there are students of varying degrees of experience and skill who transmit their knowledge of the subject to those whom they outrank and receive instruction in turn from the superior officers on the staff. Thus each member of the group assumes the function of an instructor and the responsibilities thus imposed upon him are invariably followed by a diligent search for knowledge and information which he may pass on to those whom he is expected to serve.

But let me warn that the otolaryngologist of today must assume certain educational responsibility before he commences the practice of his specialty. He must be thoroughly trained in the principles of surgery, newer surgical techniques, protein metabolism, the recognition and treatment of shock, the value of early ambulation, methods of resuscitation therapy, and the use of modern anesthetics, if he is to practice surgery of the head and neck with credit to himself and safety to his patient. Recent progress in surgery has demonstrated that the preparation of the patient has much to do with the manner in which he tolerates a surgical insult and his behavior during the period of convalescence. Too much emphasis cannot be placed upon the protein requirements of the surgical patient. The degree and rate of tissue repair are tremendously influenced by the aminoacids and any patient who is a victim of their impoverishment is destined to react poorly to a major surgical procedure.

Experience during the war taught us that the best treatment for blood loss was a transfusion of whole blood. Chemotherapy and penicillin when intelligently used are great saviors of life and limb, but are not substitutes for operations properly performed. These agents are not a compromise for a poor operation and anyone who believes that the sulfonamides used locally will compensate for mediocrity in the operating room is certain to be disillusioned. The trend now is definitely against the introduction of the chemotherapeutic agents directly into a wound.

Throughout this discussion there has been a great temptation to quote from numerous references and to pose the viewpoints of many otolaryngologists who have made creditable contributions to the literature. I wish it might have been possible to pay tribute to our living contributors and to do justice to them by expressing their critical judgments, but time obviously would not permit such an encyclopedic survey of the past century of otolaryngology. Unquestionably I have overlooked many important and significant advances during this period. If I have failed in some instances to give correct dates, it is because I have not tried to identify the time of ideas and concepts; rather have I endeavored to date the periods of changing trends and the practical application of them. If there is any justification for this long review, I hope it may be found in a deeper appreciation of the indomitable spirit and devotion of our forefathers and a motivation to the young men of today in whose hands the fate of otolaryngology is held, to strive even more sedulously for future progress.

SECTION ON MICROBIOLOGY

WEDNESDAY EVENING, APRIL 20, AT 8:30 O'CLOCK

I. EXECUTIVE SESSION

- a. Reading of the Minutes
- b. Election of Section Officers
 - For Chairman—Frank L. Horsfall, Jr.
 - For Secretary—Harry Most
- c. Election of one member of the Advisory Board
 - Gregory Shwartzman (1949-54)

- b. Clinical use of synthetic and fermentation chloromycetin
 - Joseph E. Smadel (by invitation)
 - Army Medical School
 - Washington, D. C.
- c. Clinical use of chloromycetin in certain bacterial infections
 - Theodore E. Woodward (by invitation), University of Maryland School of Medicine, Baltimore

GREGORY SHWARTZMAN

Chairman

The Mount Sinai Hospital

HARRY MOST

*Secretary*New York University
College of Medicine

II. PAPERS OF THE EVENING

- a. Chemistry of chloromycetin
 - H. M. Crooks, Jr. (by invitation)
 - Parke Davis Research Laboratories
 - Detroit, Michigan

Chemistry of Chloromycetin

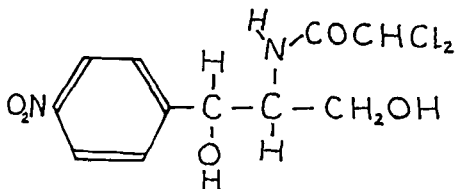
H. M. CROOKS, JR.

At the risk of being somewhat inadequate in treatment of the subject I have taken the liberty of changing the emphasis in this talk. For an audience of physicians the purely organic chemistry phases of the development of this antibiotic could be most boring. I trust I shall be forgiven for only pointing out some of the salient features of the chemistry and treating at more length the toxicologic features and the metabolism as they have been worked out by my colleagues, Drs. Gruhitz and Glazko and their groups.

In our screening of various organisms from soil samples Ehrlich and his group found that an actinomycete selected from a Venezuela soil sample by Burkholder of Yale produced a considerable antibiotic

activity which appeared to be new in its antibacterial spectrum. Moreover, it proved intriguing to the chemist, when Bartz succeeded in isolating and crystallizing the active material with a reasonable melting point of 150°, stable enough to be sublimed in high vacuum, stable over a pH range of 3 to 9 in solution and of a molecular weight, about 310, well within the range of synthesis. The compound is optically active and, from analysis, has the formula $C_{11}H_{12}N_2Cl_2O_5$. The fact that the chlorine was not ionic in nature but actually quite inert chemically was most interesting. The substance also showed a strong absorption band in the ultra-violet region. Two of our staff, Doub and Vanderbelt, have devoted considerable study to the relation of such absorp-

tion to structure. We were politely skeptical when they told us that the compound looked like a derivative of *para*-nitro-toluene. We were quite aware that nitro-groups have never been found in nature or associated with living processes excepting in a toxic manner. Our apologies were given in all humility when the structure as finally determined by Dr. Mildred Rebstock proved to be a *para*-nitrophenylpropane derivative:



Chloromycetin

D-(-)-*threo*-2-dichloroacetamido - 1 - *p*-nitrophenyl-1,3-propanediol.

Structurally the carbon skeleton shows a resemblance to *nor*-ephedrine but here again the antibiotic activity is associated with "unnatural" optical form as in penicillin with its "d" amino acid component. The Chloromycetin structure is related to *l*-pseudo-*nor*-ephedrine and not to *l*-ephedrine. The appearance of dichloroacetic acid as the amide on the side-chain was also almost as unexpected as the nitro-group.

With the knowledge that we were dealing with a nitro-phenyl compound which was a derivative of an unpleasantly corrosive organic acid you can understand that toxicity data were examined most critically. It just did not seem reasonable that Chloromycetin should be non-toxic. We will get to that story shortly.

Almost as soon as we were sure of the structure of the carbon skeleton Controulis started to work on synthesis. He acquired quite a knowledge of the difficulties of preparing a compound with a number of functional groups. The synthesis which he developed started with benzaldehyde and nitroethanol and was quite successful on a laboratory scale but presented some difficulties for large scale production. Alternate methods using a different series of

reactions and starting either from benzaldehyde or acetophenone were developed by Long and Troutmann and these are now being expanded to production scale. While consideration of the structure of the antibiotic shows that four optical forms can (and do) exist, the synthetic material now being produced is identical in all respects, physically, chemically and biologically, with the drug as produced by fermentation. It is the first practical synthesis of a major antibiotic.

To revert to the matter of toxicity, Chloromycetin has proved to be essentially non-toxic in therapeutic doses. The acute toxicity in mice, intraperitoneally in acacia suspension, shows a maximal tolerated dose of 750 mg/kg., LD₅₀ 1320 mg/kg; orally, 1500 mg/kg and 2640 mg/kg respectively. Intravenously, in rats, using a solution in 50% acetamide the maximal tolerated dose is 225 mg/kg and the LD₅₀ dose about 280 mg/kg. In dogs, orally, the tolerated dose is about 300 mg/kg and we have not yet found the dosage level which is 50% lethal. In chronic toxicity studies mice have tolerated 425 mg/kg/day for 4 weeks with the LD₅₀ level somewhere over 2060 mg/kg/day when given in the ration for two weeks. Dogs have tolerated over 200 mg/kg/day for 4 months. Again in this species we have not yet been able to reach the LD₅₀ level orally.

When administered intravenously in propylene glycol (10% solution) to anesthetized dogs at the rate of 2 cc. per minute a 100 mg/kg dose of Chloromycetin shows little effect on respiration but a definite effect on blood pressure, inducing a fall in blood pressure of the shock type.

Dogs on an oral dosage of Chloromycetin up to 100 mg/kg/day show a slight drop in erythrocyte count over a three month period, from about 6.7 to 6.0 million, hardly more than would be expected in untreated dogs bled of 100 cc. three times in the same interval.

Examination of the blood non-protein nitrogen of eleven dogs given 50-100 mg/kg/twice daily for 1½ months showed no more variation than is to be expected on a similar random group of pound animals.

Turning now to the fate of Chloromycetin

in the animal body, it was found quite early that the drug is readily absorbed when given orally and significant blood levels are obtained promptly. In dogs a level of 20 micrograms per cc. is obtained one hour after a 150 mg oral dose, a peak at about 40 micrograms is obtained at four hours which drops below 10 micrograms only after eight hours. In contrast a 50mg/kg intravenous dose starts at the 40 microgram level falling below 10 in about 3 hours. When the urine of these dogs is examined it is found that the peak excretion for orally administered drug is at about 4 to 6 hours and that only small amounts are being excreted after 20 hours. It was interesting to find that only about 3-7% of the administered activity was recoverable in the urine. On the other hand if the urine were assayed chemically to determine the nitro-compounds excreted the 150mg/kg orally dosed dog eliminated 55% of the drug in the urine.

It was found that man showed an even higher efficiency in quantitative elimination of the drug in the urine. Again an oral dose of 1500 mg. showed a peak in serum levels at about the 4 hour period, effective levels being maintained for from 6 to 8 hours. Examination of the excretion rate data after an oral dose of 500 mg. showed that roughly half had been excreted by eight hours and

only small amounts remained at 24 hours. About 7½% of the dose was recoverable as biologically active unchanged drug but 91% of the original amount of nitro-compound was recovered. Glazko and his group set about isolating the metabolized portion. It turned out to be a compound much more soluble in water than Chloromycetin and not, strictly, a degradation product. Instead of chewing the antibiotic up into little pieces where the nitro group could more readily exert its toxic effects, the animal body apparently moves it out of its system as the sodium glucuronide through conjugation of one of the hydroxyl groups with glucuronic acid, the remainder of the molecule, including the amide linkage, surviving intact.

While I have mentioned many of the workers identified with the development of Chloromycetin there have been many omissions. The nature of antibiotic research calls for an integrated team of bacteriologists, biochemists and chemists both in research and development scale and the listing here would be a long one. This glimpse of the laboratory end of the problem is, after all, the preliminary to the meat of the story, the clinical test of the drug. We hope and believe that that part will be quite as fascinating as ours.

Clinical Use of Synthetic and Fermentation Chloramphenicol (Chloromycetin)

JOSEPH E. SMADEL

The new antibiotic chloramphenicol has proven extremely useful in the treatment of a number of the rickettsial diseases of man. These include epidemic and murine typhus, scrub typhus, and Rocky Mountain spotted fever. In most of these rickettsial infections, which previously had been only moderately amenable to treatment with para-aminobenzoic acid, patients receiving chloramphenicol became afebrile in a day or so after therapy was instituted.

The new synthetic form of chlorampheni-

col, which has been studied extensively in the laboratory and on the ward, possesses the same antirickettsial properties as the fermentation type drug. Furthermore, the synthetic compound is of the same low toxicity for man as the natural material obtained from the fermentation of *Streptomyces venezuelae*. Charts illustrating the results obtained in the treatment of patients with rickettsial diseases were presented and discussed.

*Clinical Use of Chloramphenicol (Chloromycetin)
In Certain Bacterial Infections*

THEODORE E. WOODWARD

Certain diseases of bacterial origin have responded to treatment with chloramphenicol in a highly uniform and specific manner. These include typhoid fever, undulant fever and several infections of the genito-urinary tract.

Twenty-two patients with typhoid fever received chloramphenicol on the 12th day of illness (mean). The average duration of fever after receiving treatment was 3.5 days. Four patients in this series with bacterial and clinical relapses responded to retreat-

ment. Four typhoid carriers have not benefited from chloramphenicol therapy. Nine patients with acute brucellosis treated on the 33rd day of illness (mean) responded within 3 days. One patient relapsed but promptly responded to a second course of antibiotic. Patients with chronic urinary tract infection, caused by bacteria of the colon, proteus and pseudomonas groups have also benefited from treatment with this drug.

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INDEX, 1949

- Abramson, Harold A., Therapy of asthma with reference to its psychodynamic pharmacology, 345
- Accessions to the Library, Recent, 61, 130, 264, 331, 397, 537, 601, 666, 795
- Address of acceptance and appreciation of the gift of the Edwin Smith papyrus, George Baehr, 60
- of the retiring president, George Baehr, 145
- of welcome to 22nd Graduate Fortnight, advances in diagnostic methods, Benjamin P. Watson, 747
- Adlersberg, David, Newer advances in gout, 651
- Advances in diagnostic methods, Benjamin P. Watson, 747
- in our knowledge concerning the etiology and treatment of hematological disorders, Cyrus C. Sturgis, 84
- in therapy, George Baehr, 3
- in treatment of malignant disease, C. P. Rhoads, 271
- Allen, Frederic M., Discussion on Review of studies on blood sugar, 52
- Allergy and antihistamine therapy, a review, Mary Hewitt Loveless and Milton Dworin, 473
- Ambulation, Early, following surgical procedures, James B. Blodgett, 176
- Analgesic drugs, New, Henry B. van Dyke, 152
- Antiepileptic drugs, Use of, H. Houston Merritt, 5
- Anti-histamine substances, Recent advances in the domain of the, phenothiazine derivatives, B. N. Halpern, 323
- Antihistamine therapy, Allergy and, a review, Mary Hewitt Loveless and Milton Dworin, 473
- Annual meeting, January 6, 1949
- Address of the retiring president, George Baehr, 145
- Presidential address, Benjamin P. Watson, 135
- Results of operations for hyperparathyroidism, William Barclay Parsons, 285
- Appraisal of the clinical aspects of the Rh factor, Peter Vogel, 261
- Ashford, Mahlon, The New York Academy of Medicine, its first hundred years by Philip Van Ingen, a review, 741
- Asthma, Therapy of, with reference to its psychodynamic pharmacology, Harold A. Abramson, 345
- Bacteria, Relationship of, to the common cold, Yale Kneeland, Jr., 534
- Bacterial infections, Clinical use of chloromycetin in certain, Theodore E. Woodward, 795
- Baehr, George, Address of acceptance and appreciation of the gift of the Edwin Smith papyrus, 60
- Address of the retiring president, 145
- Advances in therapy, Opening address Graduate Fortnight, 1948, 3
- Bell's and other palsies, Treatment of, William Bierman, 307
- Best, Charles H., Discussion on Review of studies on blood sugar, 58
- Bierman, William, Treatment of Bell's and other palsies, 307
- Biggs (Hermann M.) Memorial Lecture, Medical, social and public health aspects of rehabilitation, Howard A. Rusk, 554
- Blodgett, James B., Early ambulation following surgical procedures, 176
- Blood sugar, Review of studies on, Edward Thomas Waters, 32
- Discussions, Frederick M. Allen, Edward M. Dillon, Thomas H. McGavack and Charles H. Best, 52
- Book review
- The New York Academy of Medicine, its first hundred years by Philip Van Ingen, review, Mahlon Ashford, 741
- Browder, Jefferson, Pain in the lumbo-

- sacral region, 434
- Bruger, Maurice and Elliot Oppenheim, Present status of liver function tests including observations on the newer flocculation procedures, 16
- Cancer research, General view of, Leonard A. Scheele, 671
- Centennial addresses
- Chronicle of one hundred years of otolaryngology, A. C. Furstenberg, 775
- Psychiatric perspectives of today, Gregory Zilboorg, 577
- Thoughts on medical history and libraries—1847 and 1947, Sanford V. Larkey, 65
- Central nervous system, Modern treatment of syphilis, including syphilis of the, Evan W. Thomas, 505
- Chemical aspects of some of the newer insecticides, H. L. Haller, 374
- Chemistry of chloromycetin, H. M. Crooks, Jr., 792
- Chloramphenicol. See Chloromycetin.
- Chloromycetin, Chemistry of, H. M. Crooks, Jr., 792
- Clinical use of synthetic and fermentation, Joseph E. Smadel, 794
- in certain bacterial infections, Clinical use of, Thomas E. Woodward, 795
- Chronicle of one hundred years of otolaryngology, A. C. Furstenberg, 775
- Clinical aspects of some of the newer insecticides, H. L. Haller, 374
- use of chloromycetin in certain bacterial infections, Theodore E. Woodward, 795
- use of synthetic and fermentation chloromycetin, Joseph E. Smadel, 794
- Clinical Research Meeting (abstracts)
- Anomalous atrioventricular excitation produced by catheterization of the normal human heart, Bertha Rader, Adolph R. Berger, Stanley A. Briller, Joseph Brumlik and Charles E. Kossmann, 444
- Association of interatrial septal defect and anomalies of the osseous system, B. S. Oppenheimer, N. S. Blackman and Arthur Grishman, 442
- Aureomycein and chloromycetin in brucellosis, Harold J. Harris, 458
- Autoantibodies in different phases of human glomerulonephritis, Kurt Lange, David Weiner, Michael M. A. Gold, Victor Tchertkoff and Vera Simon, 447
- Biological chemistry of wound healing, effect of blocking the sulfhydryl group (-SH) in vivo with iodoacetic acid, Jameson L. Chassin and S. Arthur Localio, 452
- Carbohydrate utilization in surgical patients, blood lactic acid in pre- and post-operative patients after the administration of glucose, John J. Castronuovo, 455
- Effect of an adrenolytic compound, dihydroergocornine, on epinephrine-induced stimulation of the adrenal cortex, Stanley August and Richard Gubner, 446
- Electrolyte abnormalities in chronic congestive heart failure, effects of administration of potassium and sodium salts, Charles L. Fox, Jr., Charles K. Friedberg and Abraham G. White, 461
- Ergotamine tartrate and the "2-step" exercise electrocardiogram in functional heart disturbance and in organic heart disease, Leon Pordy, Joseph Kolker, Mortimer J. Blumenthal and Arthur M. Master, 445
- Evaluation of the mumps skin-test in pediatric practice, Alfred L. Florman, Alfred E. Fischer and Ralph E. Moloshok, 441
- Fate of dicumarol in man, relationship between prothrombin time and plasma level of dicumarol, Murray Weiner, Shepard Shapiro, Julius Axelrod and Bernard B. Brodie, 449
- Hemophilioid disease, O. Herman Dreskin and Nathan Rosenthal, 457
- Hypermetabolism without hyperthyroidism, Solomon Silver, Edward B. Crohn and Philip Porto, 441
- Management of ascites due to cirrhosis of the liver, the use of "rice" diet, blood and plasma, diuretics and surgery, George F. Kamen, Max Trubek and Jere W. Lord, Jr., 454
- Method for the preparation of exteriorized skin-covered loops of intestine for the study of bowel obstruction,

- Robert T. Crowley and Donald A. Davis, 450
- New synthetic anticoagulant (heparinoid), preliminary report of its action in humans, C. W. Sorenson, Joseph Seifter and I. S. Wright, 448
- Response of gastric-dissolved mucoprotein to insulin, a new test for evaluation of secretory status of fundal glands and integrity of nervous pathways to the stomach, George B. Jerzy Glass and Linn J. Boyd, 459
- Role of proteins in the pathogenesis of renal insufficiency, Ralph M. Sussman and Selwyn Z. Freed, 462
- Significance of RS-T elevation in acute coronary insufficiency, Irving G. Kroop, Harry L. Jaffe and Arthur M. Master, 465
- Simultaneous left- and right-sided intracardiac electrocardiography in man, right bundle branch block, A. Seligmann, M. F. Steinberg, I. G. Kroop, and A. Gresham, 443
- Some limitations of vagotomy in the treatment of peptic ulcer, a critical follow-up analysis of fifty cases, Martin J. Healy, Jr. and Paul K. Sauer, 449
- Starch sponge, a hemostatic agent, Samuel S. Rosenfeld, 453
- Studies with the quantitative cephalin-cholesterol flocculation reaction, Abraham Saifer, 456
- Treatment of pernicious anemia with animal protein factor concentrates of bacterial origin, Leo M. Meyer, Norton D. Ritz, Manuel Bowen, George Bock and Julius Rutzky, 464
- Use of urinary pigment excretion for the measurement of basal metabolic rate, Jefferson J. Vorzimer, Ira B. Cohen and Jules Joskow, 462
- Committee on Public Health Relations, Report of Subcommittee on Proposed Hospital Bond Issue, 743
- on Public Health Relations of The New York Academy of Medicine, Report on Hospitalization of veterans, 587
- Common cold, Introduction to studies on the, A. R. Dochez, 528
- cold, Relationship of bacteria to the, Yale Kneeland, Jr., 534
- cold, Research on the, Norman H. Topping, 530
- Critique of the present status of the psychotherapies, Robert P. Knight, 100
- Crooks, H. M., Jr., Chemistry of chloromycetin, 792
- Diagnostic methods, Advances in, Benjamin P. Watson, 747
- significance of electrolyte disturbances, John P. Peters, 749
- Dillon, Edward S., Discussion on Review of studies on blood sugar, 54
- Doan, Charles A., Hypersplenism, 625
- Dochez, A. R., Introduction to studies on the common cold, 528
- Drugs, Safeguards in the use of new, Austin Smith, 115
- Dworin, Milton, Mary Hewitt Loveless and, Allergy and antihistamine therapy, a review, 473
- Early ambulation following surgical procedures, James B. Blodgett, 176
- Edwin Smith papyrus. See Smith (Edwin) papyrus.
- Electric shock therapy, Present status of, Lothar B. Kalinowsky, 541
- Electroencephalography, Present status of clinical, Frederic A. Gibbs, 764
- Electrolyte disturbances, Diagnostic significance of, John P. Peters, 749
- studies in surgical patients, Place of, John S. Lockwood and H. T. Randall, 228
- Entomology, Recent advances in medical and veterinary, E. F. Knipling, 388
- Evaluation of the surgical treatment of hypertension, R. H. Smithwick, 698
- Ewing (James) Memorial Lecture, General view of cancer research, Leonard A. Scheele, 671
- Friday Afternoon Lectures
- Iron metabolism and hemochromatosis, S. Granick, 403
- Modern treatment of syphilis, including syphilis of the central nervous system, Evan W. Thomas, 505
- Newer advances in gout, David Adlersberg, 651

- Pain in the lumbosacral region, Jefferson Browder, 434
- Recent advances in our knowledge concerning the nephrotic syndrome, David Seegal and Arthur R. Wertheim, 605
- Therapy of asthma with reference to its psychodynamic pharmacology, Harold A. Abramson, 345
- Friends of the Rare Book Room of the Library of The New York Academy of Medicine, Progress report, 194
- Furstenberg, A. C., Chronicle of one hundred years of otolaryngology, 775
- General view of cancer research, Leonard A. Scheele, 671
- Gibbs, Frederic A., Present status of clinical electroencephalography, 764
- Goodhart, Robert S., Principles of nutrition therapy, 185
- Gout, Newer advances in, David Adlersberg, 651
- Graduate Fortnight, 1948
- Advances in our knowledge concerning the etiology and treatment of hematological disorders, Cyrus C. Sturgis, 84
- Advances in treatment of malignant disease (Ludwig Kast Lecture), C. P. Rhoads, 271
- Allergy and antihistamine therapy, a review, Mary Hewitt Loveless and Milton Dworin, 473
- Critique of the present status of the psychotherapies, Robert P. Knight, 100
- Early ambulation following surgical procedures, James B. Blodgett, 176
- Evaluation of the surgical treatment of hypertension, R. H. Smithwick, 698
- Management of acute renal failure, I. Snapper, 199
- Medical and surgical treatment of peptic ulcer, Chester M. Jones, 488
- New analgesic drugs, Henry B. van Dyke, 152
- Opening address, Advances in therapy, George Baehr, 3
- Principles of nutrition therapy, Robert S. Goodhart, 185
- Recent advances in the domain of the anti-histamine substances, phenothiazine derivatives, B. N. Halpern, 323
- Recent advances in the therapy of the more common protozoan and helminthic infections of man, Harry Most, 717
- Safeguards in the use of new drugs, Austin Smith, 115
- Therapeutic role of procaine and its derivatives, E. A. Rovenstine and E. M. Papper, 298
- Treatment of Bell's and other palsies, William Bierman, 307
- Use of antiepileptic drugs, H. Houston Merritt, 5
- Graduate Fortnight, 1949
- Address of welcome, advances in diagnostic methods, Benjamin P. Watson, 747
- Announcement, 470
- Diagnostic significance of electrolyte disturbances, John P. Peters, 749
- Present status of clinical encephalography, Frederic A. Gibbs, 764
- Granick, S., Iron metabolism and hemochromatosis, 403
- Guthrie, Douglas, Rise and progress of medical education in Scotland, 521
- Haller, H. L., Chemical aspects of some of the newer insecticides, 374
- Halpern, B. N., Recent advances in the domain of the anti-histamine substances, phenothiazine derivatives, 323
- Heath, Robert G. and John J. Weber, J. Lawrence Pool, Topectomy, surgical indications and results, 335
- Helminthic infections of man, Recent advances in the therapy of the more common protozoan and, Harry Most, 717
- Hematological disorders, Advances in our knowledge concerning the etiology and treatment of, Cyrus C. Sturgis, 84
- Hemochromatosis, Iron metabolism and, S. Granick, 403
- Hitler, Medicine under, George Rosen, 125
- Hospital Bond Issue, Subcommittee on Proposed, Report of, 743
- Hospitalization of veterans, Report by the Committee on Public Health Relations of The New York Academy of Medicine, 587
- Hyperparathyroidism, Results of operations for, William Barclay Parsons, 285

- blood types, Alexander S. Wiener, 255
- Recent advances in medical and veterinary entomology, E. F. Knipling, 388
- Recent views on the genetics of the Rh-Hr blood factors, Herluf H. Strandkov, 249
- Relationship of bacteria to the common cold, Yale Kneeland, Jr., 534
- Research on the common cold, Norman H. Topping, 530
- Rh factor, general significance and methods of study, Philip Levine, 244
- Modern treatment of syphilis, including syphilis of the central nervous system, Evan W. Thomas, 505
- Most, Harry, Recent advances in the therapy of the more common protozoan and helminthic infections of man, 717
- Movements, Concerning voluntary and involuntary, Abraham M. Rabiner, 566
- Mussolini, Medicine under, Mario Volterra, 364
- Nephrotic syndrome, Recent advances in our knowledge concerning the, David Seegal and Arthur R. Wertheim, 605
- New analgesic drugs, Henry B. van Dyke, 152
- New York Academy of Medicine (The), its first hundred years by Philip Van Ingen, a review, Mahlon Ashford, 741
- Newer advances in gout, David Adlersberg, 651
- Nutrition therapy, Principles of, Robert S. Goodhart, 185
- Obituary, Eugene Hillhouse Pool—1874—1949, Frank J. McGowan, 466
- Oppenheim, Elliot, Maurice Bruger and, Present status of liver function tests including observations on the newer flocculation procedures, 16
- Otolaryngology, Chronicle of one hundred years of, A. C. Furstenberg, 775
- Pain in the lumbosacral region, Jefferson Browder, 434
- Palsies, Treatment of Bell's and other, William Bierman, 307
- Papper, E. M., E. A. Rovenstine and, Therapeutic role of procaine and its derivatives, 298
- Papyrus. See Smith (Edwin) papyrus.
- Parsons, William Barclay, Results of operations for hyperparathyroidism, 285
- Peptic ulcer, Medical and surgical treatment of, Chester M. Jones, 488
- Pernicious anemia, Present status of vitamin B₁₂ in, Edward H. Reisner, Jr., 429
- Peters, John P., Diagnostic significance of electrolyte disturbances, 749
- Phenothiazine derivatives, Recent advances in the domain of the anti-histamine substances, B. N. Halpern, 323
- Place of electrolyte studies in surgical patients, John S. Lockwood and H. T. Randall, 228
- Pool, Eugene Hillhouse—1874-1949, Obituary, Frank J. McGowan, 466
- Pool, J. Lawrence, Robert G. Heath and John J. Weber, Topectomy, surgical indications and results, 335
- Present status of clinical electroencephalography, Frederic A. Gibbs, 761
- status of electric shock therapy, Lothar B. Kalinowsky, 541
- status of liver function tests including observations on the newer flocculation procedure, Maurice Bruger and Elliot Oppenheim, 16
- status of vitamin B₁₂ in pernicious anemia, Edward H. Reisner, Jr., 429
- President, Address of the retiring, George Baehr, 145
- Presidential address, Benjamin P. Watson, 135
- Principles of nutrition therapy, Robert S. Goodhart, 185
- Procaine and its derivatives, Therapeutic role of, E. A. Rovenstine and E. M. Papper, 298
- Protozoan and helminthic infections of man, Recent advances in the therapy of the more common, Harry Most, 717
- Psychiatric perspectives of today, Gregory Zilboorg, 577
- Psychotherapies, Critique of the present status of the, Robert P. Knight, 100
- Rabiner, Abraham M., Concerning voluntary and involuntary movements, 566

- Randall, H. T., John S. Lockwood and, Place of electrolyte studies in surgical patients, 228
- Recent advances in the domain of the anti-histamine substances, phenothiazine derivatives, B. N. Halpern, 323
- advances in our knowledge concerning the nephrotic syndrome, David Seegal and Arthur R. Wertheim, 605
- advances in medical and veterinary entomology, E. F. Knipling, 388
- advances in the therapy of the more common protozoan and helminthic infections of man, Harry Most, 717
- views on the genetics of the Rh-Hr blood factors, Herlaf H. Strandkov, 249
- Rehabilitation, Medical, social and public health aspects of, Howard A. Rusk, 554
- Reisner, Edward H., Jr., Present status of vitamin B₁₂ in pernicious anemia, 429
- Relationship of bacteria to the common cold, Yale Kneeland, Jr., 534
- Renal failure, Management of acute, I. Snapper, 199
- Report of Subcommittee on Proposed Hospital Bond Issue, 743
- Research on the common cold, Norman H. Topping, 530
- Results of operations for hyperparathyroidism, William Barclay Parsons, 285
- Review of studies on blood sugar, Edward Thomas Waters, 32
- Discussions, Frederick M. Allen, Edward S. Dillon, Thomas H. McGavack and Charles H. Best, 52
- Rh factor, Appraisal of the clinical aspects of the, Peter Vogel, 261
- factor, general significance and methods of study, Philip Levine, 244
- Rh-Hr blood factors, Recent views on the genetics of the, Herlaf H. Strandkov, 249
- blood types, Medicolegal aspects of the, Alexander S. Wiener, 255
- Rhoads, C. P., Advances in treatment of malignant disease, 271
- Rise and progress of medical education in Scotland, Douglas Guthrie, 521
- Rosen, George, Medicine under Hitler, 125
- Rovenstine, E. A. and E. M. Papper, Therapeutic role of procaine and its derivatives, 298
- Rusk, Howard A., Medical, social and public health aspects of rehabilitation, 554
- Safeguards in the use of new drugs, Austin Smith, 115
- Scheele, Leonard A., General view of cancer research, 671
- Scotland, Rise and progress of medical education in, Douglas Guthrie, 521
- Seegal, David and Arthur R. Wertheim, Recent advances in our knowledge concerning the nephrotic syndrome, 605
- Smadel, Joseph E., Clinical use of synthetic and fermentation chloromycetin, 794
- Smith, Austin, Safeguards in the use of new drugs, 115
- Smith (Edwin) papyrus, Address of acceptance and appreciation of the gift of the, George Baehr, 60
- Smithwick, R. H., Evaluation of the surgical treatment of hypertension, 698
- Snapper, I., Management of acute renal failure, 199
- Strandkov, Herlaf H., Recent views on the genetics of the Rh-Hr blood factors, 249
- Sturgis, Cyrus C., Advances in our knowledge concerning the etiology and treatment of hematological disorders, 84
- Subcommittee on Proposed Hospital Bond Issue, Report of, 743
- Surgical patients, Place of electrolyte studies in, John S. Lockwood and H. T. Randall, 228
- procedures, Early ambulation following, James B. Blodgett, 176
- treatment of hypertension, Evaluation of, R. H. Smithwick, 698
- treatment of peptic ulcer, Medical and, Chester M. Jones, 488
- Syphilis, Modern treatment of, including syphilis of the central nervous system, Evan W. Thomas, 505
- Therapeutic role of procaine and its derivatives, E. A. Rovenstine and E. M. Papper, 298
- Therapy, Advances in, George Baehr, 3
- of asthma with reference to its psychodynamic pharmacology, Harold A. Abramson, 345
- Thomas, Evan W., Modern treatment

- syphilis, including syphilis of the central nervous system, 505
- Thoughts on medical history and libraries—1817 and 1947, Sanford V. Larkey, 65
- Topectomy, surgical indications and results, J. Lawrence Pool, Robert G. Heath and John J. Weber, 335
- Topping, Norman H., Research on the common cold, 530
- Treatment of Bell's and other palsies, William Bierman, 307
- Use of antiepileptic drugs, H. Houston Merritt, 5
- Van Dyke, Henry B., New analgesic drugs, 152
- Van Ingen, Philip, The New York Academy of Medicine, its first hundred years, a review, Mahlon Ashford, 741
- Veterans, Hospitalization of, Report by the Committee on Public Health Relations of The New York Academy of Medicine, 587
- Vitamin B₁₂ in pernicious anemia, Present status of, Edward H. Reisner, Jr., 429
- Vogel, Peter, Appraisal of the clinical aspects of the Rh factor, 261
- Volterra, Mario, Medicine under Mussolini, 364
- Voluntary and involuntary movements, Concerning, Abraham M. Rabiner, 566
- Waters, Edward Thomas, Review of studies on blood sugar, 32
- Watson, Benjamin P., Address of welcome to 22nd Graduate Fortnight; advances in diagnostic methods, 747
Presidential address, 135
- Weber, John J., J. Lawrence Pool, Robert G. Heath and, Topectomy, surgical indications and results, 335
- Wertheim, Arthur R., David Seegal and, Recent advances in our knowledge concerning the nephrotic syndrome, 605
- Wiener, Alexander S., Medicolegal aspects of the Rh-Hr blood types, 255
- Woodward, Theodore E., Clinical use of chloromycetin in certain bacterial infections, 795
- Zilboorg, Gregory, Psychiatric perspectives of today, 577

